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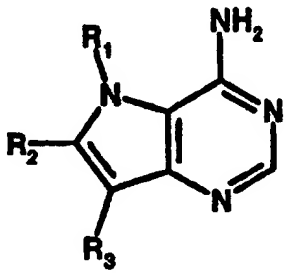
(54) Title: SUBSTITUTED 7-AMINO-PYRROLO[3,2-d]PYRIMIDINES AND THE USE THEREOF

(57) Abstract

Pyrrolo[3,2-d]pyrimidines of formula (I) wherein R_1, R_2 and R_3, are as defined in the description, are described. The compounds have valuable pharmaceutical properties and are effective especially as tyrosine protein kinase inhibitors. They can be used in warm-blooded animals in the treatment of bone diseases and other diseases that are favourably influenced by the inhibition of tyrosine protein kinase.



(I)

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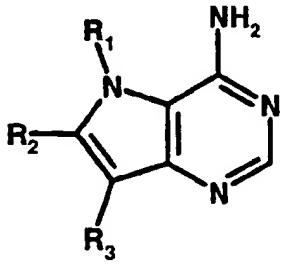
Substituted 7-amino-pyrrolo[3,2-d]pyrimidines and the use thereof

The invention relates to compounds of formula I



(I)

wherein

R_1 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl or cyclo-lower hydrocarbyl-lower alkyl, unsubstituted or substituted aryl or aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl or hetero-lower cyclyl-lower alkyl;

R_2 is hydrogen, lower alkyl or halogen;

R_3 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl or cyclo-lower hydrocarbyl-lower alkyl, unsubstituted or substituted aryl or aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl or hetero-lower cyclyl-lower alkyl;

and salts thereof.

Within the context of the present Application, the general terms used hereinbefore and hereinafter preferably have the following definitions:

The term "lower " denotes a radical having up to and including 7, and especially up to and including 6, carbon atoms.

Lower alkyl is, for example, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, neopentyl, *n*-hexyl or *n*-heptyl, preferably ethyl or methyl.

Alkyl is straight-chain or branched. On its own, for example lower alkyl, or as a constituent of other groups, for example lower alkoxy, lower alkylcarbonyl, lower alkoxycarbonyl, lower alkylaminocarbonyl, di-lower alkylaminocarbonyl, it may be unsubstituted or mono- or poly-substituted, for example by halogen, hydroxy, lower alkoxy, trifluoromethyl or by imidazolyl, and is preferably unsubstituted or substituted by halogen, hydroxy, lower alkoxy, amino, N-lower alkylamino or by N,N-di-lower alkylamino. In hetero-substituted alkyl, the carbon chain is interrupted by one or more, identical or different hetero atoms, for example by oxygen, sulfur or $S(O_2)$, especially oxygen.

Cyclo-lower hydrocarbyl denotes saturated or mono- or poly-unsaturated carbocyclic rings, preferably having from 3 up to and including 7 ring members, especially 5 or 6 ring members, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl. Cyclo-lower hydrocarbyl-lower alkyl is, for example, cyclopentylmethyl, cyclopentenylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, cyclohexenylethyl. Cyclo-lower hydrocarbyl and cyclo-lower hydrocarbyl-lower alkyl may be unsubstituted or mono- or poly-substituted, for example by hydroxy, lower alkyl, lower alkoxy, hydroxy-lower alkyl, hydroxy-lower alkoxy, halo-lower alkyl, halo-lower alkoxy, lower alkoxy-lower alkoxy, amino-lower alkyl, amino-lower alkoxy, lower alkylamino-lower alkyl, lower alkylamino-lower alkoxy, N,N-di-lower alkylamino-lower alkyl, N,N-di-lower alkylamino-lower alkoxy, N,N-hydroxy-lower alkyl-lower alkylamino-lower alkyl or by N,N-hydroxy-lower alkyl-lower alkylamino-lower alkoxy, and preferably is unsubstituted.

Aryl is, for example, phenyl or naphthyl, each of which is unsubstituted or substituted, for example as indicated hereinafter for phenyl. Aryl is preferably phenyl unsubstituted or substituted by one or more, for example from one to three, especially one or two, substituents from the group consisting of hydroxy, lower alkyl, halo-lower alkyl, (hydroxy or lower alkanoyloxy)-lower alkyl, lower alkoxy-lower alkyl, (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkoxy-lower alkyl, (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkoxy-lower alkyl, (amino or lower alkanoylamino)-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl; azacycloalkyl-lower alkyl, for example (piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl)-lower alkyl; azaheteroaryl-lower alkyl, for example (imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl)-lower alkyl, (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkylamino-lower alkyl, (amino, lower alkylamino,

di-lower alkylamino or lower alkanoylamino)-lower alkylamino-lower alkyl; azacycloalkyl-lower alkylamino-lower alkyl, for example (piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl)-lower alkylamino-lower alkyl; azaheteroaryl-lower alkylamino-lower alkyl, for example (imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl)-lower alkylamino-lower alkyl; mercapto-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, aminocarbonyl-lower alkyl, N-lower alkylaminocarbonyl-lower alkyl, N,N-di-lower alkylaminocarbonyl-lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, C_1-C_3alkylenedioxy, phenyl-lower alkoxy, (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkoxy, (amino or lower alkanoylamino)-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy; azacycloalkyl-lower alkoxy, for example (piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl)-lower alkoxy; azaheteroaryl-lower alkoxy, for example (imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl)-lower alkoxy; (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkylamino-lower alkoxy, (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkylamino-lower alkoxy; azacycloalkyl-lower alkylamino-lower alkoxy, for example (piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl)-lower alkylamino-lower alkoxy; azaheteroaryl-lower alkylamino-lower alkoxy, for example (imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl)-lower alkylamino-lower alkoxy; (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkoxy-lower alkoxy, (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkoxy-lower alkoxy, (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkoxy, (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkoxy, hydroxysulfonyl-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, aminocarbonyl-lower alkoxy, N-lower alkylaminocarbonyl-lower alkoxy, N,N-di-lower alkylaminocarbonyl-lower alkoxy, amino, lower alkylamino, di-lower alkylamino, lower alkanoylamino; azacycloalkyl, for example piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl; azaheteroaryl, for example imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl; mercapto, lower alkyl-(thio, sulfinyl or sulfonyl), (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkyl-(thio, sulfinyl or sulfonyl), (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkyl-(thio, sulfinyl or sulfonyl), (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkoxy-lower alkyl-(thio, sulfinyl or sulfonyl), (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkoxy-lower alkyl-(thio, sulfinyl or sulfonyl), (hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkylamino-lower

alkyl-(thio, sulfinyl or sulfonyl), (amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkylamino-lower alkyl-(thio, sulfinyl or sulfonyl), carboxy-lower alkylthio, lower alkoxycarbonyl-lower alkylthio, aminocarbonyl-lower alkylthio, N-lower alkylaminocarbonyl-lower alkylthio, N,N-di-lower alkylaminocarbonyl-lower alkylthio, halogen, carboxy, lower alkoxycarbonyl, aminocarbonyl, N-lower alkylaminocarbonyl, N-[(hydroxy, lower alkoxy or lower alkanoyloxy)-lower alkyl]-aminocarbonyl, N-[(amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino)-lower alkyl]-aminocarbonyl; [azacycloalkyl-lower alkyl]-aminocarbonyl, for example N-[(piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl)-lower alkyl]-aminocarbonyl; [azaheteroaryl-lower alkyl]-aminocarbonyl, for example N-[(imidazolyl, triazolyl, pyridyl, pyrimidinyl or pyrrolyl)-lower alkyl]-aminocarbonyl; N-(hydroxysulfonyl-lower alkyl)-aminocarbonyl, N,N-di-lower alkylaminocarbonyl, cyano, amidino, formamidino and guanidino and, for example, nitro, lower alkanoyl and benzoyl.

In substituents containing groups such as, for example, hydroxy-lower alkoxy, amino-lower alkoxy, hydroxy-lower alkylamino, amino-lower alkylamino, hydroxy-lower alkylthio or amino-lower alkylthio, the two hetero atoms are preferably separated from one another by at least two carbon atoms; in other words, the lower alkyl moiety is preferably so selected that there are at least two carbon atoms between the two hetero atoms.

Halogen is, for example, chlorine, bromine or fluorine, but may also be iodine.

Hetero-lower cyclyl is a saturated, mono- or poly-unsaturated or aromatic radical having from 3 up to and including 7 ring atoms, especially from 3 up to and including 6 ring atoms, wherein at least one of the ring atoms is a hetero atom, preferably nitrogen, oxygen or sulfur. Especially preferred are aza-lower cycloalkyl and aza-heteroaryl, that is to say hetero-lower cyclyl radicals that contain at least one nitrogen ring atom. When a hetero-cyclyl radical contains more than one ring hetero atom, the hetero atoms may be identical or different; one ring hetero atom is preferred. Hetero-lower cyclyl is, for example, piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, furanyl, tetrahydrofuran, thiophenyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyranyl, thiopyranyl, pyridyl, pyrrolyl or tetrazolyl.

The compounds I and their salts may be in the form of one of the possible isomers, for example stereoisomers, diastereoisomers or tautomers, or in the form of a mixture thereof. There are obtainable as pure isomers, for example, pure enantiomers, pure diastereo-

isomers or, where appropriate, pure tautomers. Accordingly, isomeric mixtures may be in the form of, for example, racemates or diastereoisomeric mixtures.

Salts of compounds of formula I are especially pharmaceutically acceptable salts, especially acid addition salts with suitable mineral acids, such as hydrohalic acids, sulfuric acid or phosphoric acid, for example hydrochlorides, hydrobromides, sulfates, hydrogen sulfates or phosphates, salts with suitable aliphatic or aromatic sulfonic acids or N-substituted sulfamic acids, for example methanesulfonates, benzenesulfonates, p-toluenesulfonates or N-cyclohexylsulfamates (cyclamates), or salts with strong organic carboxylic acids, such as lower alkanecarboxylic acids or saturated or unsaturated or hydroxylated aliphatic dicarboxylic acids, for example acetates, oxalates, malonates, maleates, fumarates, tartrates or citrates.

Also possible, where the compounds of formula I contain an acid group, are corresponding salts with bases, for example corresponding alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, pharmaceutically acceptable transition metal salts, such as zinc or copper salts, or salts with ammonia or organic amines, such as cyclic amines, mono-, di- or tri-lower alkylamines, hydroxy-lower alkylamines, for example mono-, di- or tri-hydroxy-lower alkylamines, hydroxy-lower alkyl-lower alkyl-amines or poly-hydroxy-lower alkylamines. Cyclic amines are, for example, morpholine, thiomorpholine, piperidine or pyrrolidine. Suitable mono-lower alkylamines are, for example, ethyl- and *tert*-butyl-amine; suitable di-lower alkylamines are, for example, diethyl- and diisopropyl-amine and suitable tri-lower alkylamines are, for example, trimethyl- and triethyl-amine. Suitable hydroxy-lower alkylamines are, for example, mono-, di- and tri-ethanolamine; hydroxy-lower alkyl-lower alkyl-amines are, for example, N,N-dimethylamino- and N,N-diethylamino-ethanol. Compounds of formula I having an acid group, for example carboxy, and a basic group, for example amino, may also be in the form of, for example, internal salts, i.e. in zwitterionic form, or part of the molecule may be in the form of an internal salt and another part in the form of a normal salt. Pharmaceutically unacceptable salts are also included, since they can be used, for example, for the isolation and/or purification of free compounds I and the pharmaceutically acceptable salts thereof.

The compounds of formula I have valuable pharmacological properties. In particular, they inhibit the activity of tyrosine protein kinase $pp60^{c\text{-}src}$ in concentrations of from approximately 0.001 to approximately 10 µM [test description: K. Farley *et al.*, *Anal. Biochem.* **203** (1992)

151-157; purified enzyme - as described in N. B. Lydon *et al.*, *Biochem. J.* **287** (1992) 985-993 - is used].

It is known that both targeted modification of the c-src gene, leading to the elimination of c-src, and inhibition of the activity of tyrosine protein kinase $pp60^{c\text{-}src}$ affect the bone absorption ability of osteoclasts [for elimination of c-src by gene manipulation: see, for example, P. Soriano *et al.*, *Cell* **64** (1991) 693-702; for inhibition of the activity of tyrosine protein kinase $pp60^{c\text{-}src}$: see, for example, B.F. Boyce *et al.*, *J. Clin. Invest.* **90** (1992) 1622-1627; T. Yoneda *et al.*, J. Clin. Invest. 91 (1993) 2791-2795].

Owing to their inhibitory activity against tyrosine protein kinase $pp60^{c\text{-}src}$, the compounds of formula I are therefore capable of inhibiting the bone absorption ability of osteoclasts. That can be demonstrated, for example, in the bone slice assay on bovine cortical bone platelets with rat osteoclasts in concentrations of from approx. 0.001 to approx. 10 µM. [The "bone slice assay" is described, for example, in *Biochem. Biophys. Res. Comm.* **188** (1992) 1097-1103]. In that assay, the compounds of formula I inhibit the formation of characteristic absorption holes in bone platelets *in vitro*.

In vivo, the effectiveness of compounds of formula I can be demonstrated, for example, in the Hock model in the rat. In that test, the compounds of formula I - when administered once a day *per os* in concentrations of from approx. 1 to approx. 100 mg/kg of body weight - for from 3 to 4 weeks completely or at least partially inhibit the bone loss produced as a result of ovariectomy in rats [the "Hock model" is described, for example, in *Metab. Bone Dis.* 5 (1984) 177-181].

The *in vivo* activity of compounds of formula I can also be demonstrated, for example, *via* calcium metabolism in intact rats. In that method, after i.v. injection of the test compound acute hypocalcaemia is induced within from 1 to 4 hours; it is demonstrated by determining the concentration of calcium in the blood plasma. The observation of acute hypocalcaemia can be interpreted as indirect evidence that the test compound inhibits bone absorption.

The compounds of formula I are therefore very suitable for the treatment of diseases that are responsive to inhibition of the activity of tyrosine protein kinase $pp60^{c\text{-}src}$. Special

mention may be made here of osteoporosis, and of other diseases in the course of which the absorption of bone by osteoclasts plays a role, such as tumour-induced hypercalcaemia or Paget's disease, or the treatment of bone metastases, and also inflammatory processes in joints and bones and degenerative processes in cartilage tissue. In addition, the compounds of formula I are useful in the treatment of benign or malignant tumours that are responsive to inhibition of tyrosine protein kinase $pp60^{c\text{-}src}$, such as breast cancer (mammary carcinoma) or intestinal cancer (colon carcinoma). They are capable of effecting tumour regression and of preventing the formation of tumour metastases and the growth of micrometastases. The compounds of formula I are also useful in the treatment of cardiovascular disorders, such as thrombosis.

The compounds of formula I also inhibit the activity of other non-receptor tyrosine protein kinases, such as (a) other members of the src family, for example lck and fyn, (b) abl kinase and (c) ZAP70 kinase. Furthermore, the compounds of formula I also inhibit the activity of receptor tyrosine protein kinases, such as (a) the EGF family, for example the EGF receptor, c-erbB2, c-erbB3 and c-erbB4, and (b) the PDGF family, for example the PDGF receptor, CSF-1, Kit, VEGF and FGF. Owing to those actions, the compounds of formula I can also be used in immunomodulation and in the treatment of diseases of the immune system, for example in the case of inflammations or organ transplants. They are also suitable for the treatment of (hyper)proliferative diseases, such as psoriasis, tumours, carcinomas and leukaemias, and in fibrosis and restenosis. The compounds of formula I can also be used in the treatment of diseases of the central or the peripheral nervous system where signal transmission by at least one tyrosine protein kinase is involved.

The invention relates preferably to compounds of formula I wherein
R_1 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl;
R_2 is hydrogen, lower alkyl or halogen;
R_3 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, unsubstituted or substituted aryl or aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl;
and salts thereof.

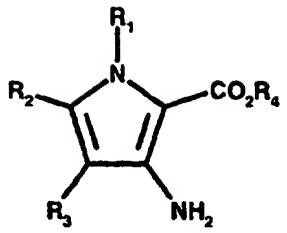
The invention relates especially to compounds of formula I wherein
R_1 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl;
R_2 is hydrogen, lower alkyl or halogen;
R_3 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, or unsubstituted or substituted aryl;
and salts thereof.

The invention relates more especially to compounds of formula I wherein
R_1 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl;
R_2 is hydrogen;
R_3 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, or unsubstituted or substituted aryl;
and salts thereof.

The invention relates most especially to compounds of formula I wherein
R_1 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl;
R_2 is hydrogen;
R_3 is unsubstituted or substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, or unsubstituted or substituted aryl;
and pharmaceutically acceptable salts thereof.

The invention relates especially to the specific compounds described in the Examples and to salts thereof.

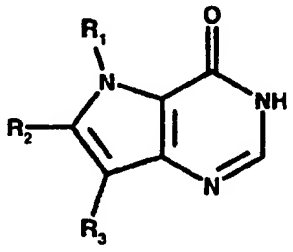
The compounds of formula I can be prepared in a manner known *per se*, for example by
a) subjecting a compound of formula II



(II)

wherein

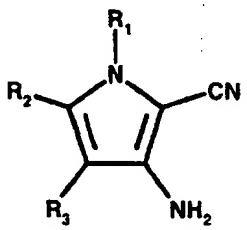
R_1, R_2 and R_3 are as defined above, and R_4 is lower alkyl, to a ring-closure reaction, with the formation of the pyrimidine ring, to give a compound of formula III



(III)

and replacing the oxygen by NH_2 by means of an exchange reaction; or

b) subjecting a compound of formula IV

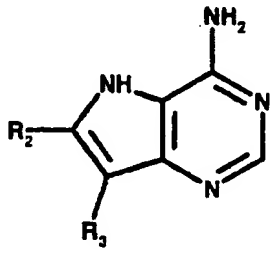


(IV)

wherein

R_1, R_2 and R_3 are as defined above, to a ring-closure reaction with the formation of the pyrimidine ring; or

c) reacting a compound of formula V



(V)

wherein R_2 and R_3 are as defined above, with a compound of formula VI

$$R_1—X \qquad (VI)$$

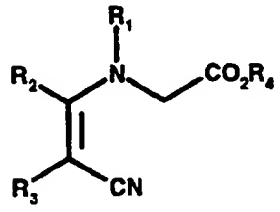
wherein R_1 is as defined above and X is a leaving group;

and, if desired, converting a compound of formula I into a different compound of formula I, and/or, if desired, converting a resulting salt into the free compound or into a different salt, and/or, if desired, converting a resulting free compound of formula I having salt-forming properties into a salt.

In the more detailed description of the processes which follows, unless indicated otherwise each of the symbols R_1-R_4 is as defined for formulae I to VI.

Process (a): The reaction according to process (a) corresponds to the cyclisation known *per se* of 3-amino-2-alkoxycarbonyl-pyrroles to 4-oxo-pyrrolo[3,2-d]pyrimidines. Suitable cyclisation reagents are the sequence 1. N,N-di-lower alkylformamide di-lower alkyl acetal and 2. ammonia. Preferred N,N-di-lower alkylformamide di-lower alkyl acetals are di-lower alkyl acetals of N,N-dimethylformamide, especially N,N-di-lower alkylformamide dineopentyl acetal. The reaction of compounds of formula II is preferably effected at elevated temperatures, for example at the reflux temperature of the reaction mixture. The reaction can be carried out with or without solvent, but preferably takes place in an aprotic solvent or solvent mixture. The resulting dialkylamino-methyleneaminoalkoxycarbonyl-pyrroles are then cyclised with ammonia to form a compound of formula III. The latter reaction is preferably effected in a polar solvent or solvent mixture in a bomb tube at ambient temperature or slightly elevated temperature whereby also one of the reactants may serve as solvent or component of a solvent mixture. The 4-oxo group can then be replaced in a manner known *per se* by halogen, especially chlorine, by reaction with a phosphorus oxytrihalide, preferably phosphorus oxytrichloride. The reaction can be carried out with or without solvent, but preferably takes place without solvent at distinctly elevated temperature, for example at 100°C to 120°C. Subsequently, the 4-halide can be replaced by $-NH_2$ by treating the reaction product with ammonia. That reaction is generally carried out at relatively high temperatures, for example at 130°C in an autoclave.

The compounds of formula II are preferably prepared using one of the known methods of pyrrole synthesis. They are obtained, for example, by cyclising a compound of formula IIa



(IIa),

preferably in the presence of a base, for example sodium ethanolate/ethanol.

Process (b): The reaction according to process (b) corresponds to the cyclisation known *per se* of 2-amino-3-cyano-pyrroles to 4-amino-pyrrolo[2,3-d]pyrimidines. Suitable cyclisation reagents are, for example, (1) formamide or (2) 1. trialkyl orthoformate/2. ammonia. The cyclisation of compounds of formula IV with formamide is preferably carried out at elevated temperature, for example at 160°C, and advantageously with the addition of a small amount of dimethylformamide and formic acid. The reaction of compounds of formula IV with trialkyl orthoformate to give the corresponding alkoxy formimidates formed as intermediates normally takes place at less elevated temperatures, for example at from 80 to 140°C. The reaction of the latter with ammonia can then be carried out generally at relatively low temperatures, for example at ambient temperature. The cyclisation then takes place preferably with base catalysis, especially using sodium ethanolate/ethanol, once again at elevated temperature, for example at the reflux temperature of the reaction mixture.

Process (c): Suitable leaving groups are, for example, methanesulfonates or p-toluenesulfonates of hydroxy compounds and halogen. The preparation of suitable pyrrolo[3,2-d]-pyrimidines of formula V is known from the literature or can be carried out analogously to the methods described in the literature. The reaction of compounds of formula V with compounds of formula VI is carried out in a manner known *per se*. For example, a methanesulfonate of formula VI is reacted with a pyrrolo[3,2-d]pyrimidine of formula V in the presence of a base, for example potassium carbonate. The reaction is preferably carried out at elevated temperature, for example at from 50°C to the reflux temperature of the reaction mixture, especially at from 60 to 80°C, and advantageously in an inert solvent or solvent mixture. The reaction can be accelerated in an advantageous manner by the addition of a suitable crown ether. In a further process, the reaction takes place in a manner

known *per se* under the conditions of phase transfer catalysis (E.V. Dehmlow and S. S. Dehmlow, *Phase Transfer Catalysis*, 3rd ed., VCH, Weinheim, 1993). The reactants of formulae V and VI are dissolved in a suitable inert solvent or solvent mixture, and the second phase is formed by a concentrated aqueous alkali metal hydroxide solution, for example 30 % sodium hydroxide solution. Advantageously, a phase transfer catalyst, for example a quaternary ammonium halide, such as tetrabutylammonium bromide, is added.

In a variant of process (c), a compound of formula III wherein R_1 is hydrogen, or a corresponding compound obtainable by replacing the 4-oxo group by halogen, is used as starting material and reacted with a compound of formula VI, and then the 4-amino group is introduced as described in process (a).

Compounds of formula I can be converted into other compounds of formula I. For example, in a manner known *per se* substituents in the aryl radical R_1 can be converted into one another.

For example, halo-lower alkyl, e.g. chloromethyl, can be reacted, for example, with unsubstituted or substituted lower alkanols, lower alkanethiols or lower alkylamines in accordance with a nucleophilic substitution reaction, yielding unsubstituted or substituted lower alkoxy-lower alkyl, lower alkylthio-lower alkyl or lower alkylamino-lower alkyl, respectively.

Hydroxy can be reacted, for example, with unsubstituted or substituted halo-lower alkanes, yielding unsubstituted or substituted lower alkoxy. Hydroxy can, for example, also be reacted first with a di-halo-lower alkane, for example 1-bromo-2-chloroethane, yielding Ω-halo-lower alkoxy; the latter can be reacted in a manner analogous to that described above with unsubstituted or substititued lower alkanols, lower alkanethiols or lower alkylamines in accordance with a nucleophilic substitution reaction, yielding unsubstituted or substituted lower alkoxy-lower alkoxy, lower alkylthio-lower alkoxy or lower alkylamino-lower alkoxy, respectively.

Analogously to hydroxy, mercapto can also be alkylated as described in the preceding paragraph.

Lower alkylthio groups can be converted by controlled oxidation both into lower alkylsulfinyl groups and into lower alkylsulfonyl groups.

Amino groups and hydroxy groups can be acylated in known manner, yielding, for example, lower alkanoylamino and lower alkanoyloxy groups, respectively.

Carboxylic acid radicals can be converted in accordance with known derivatisation methods, such as esterification or amide formation, into carboxylic acid derivatives, such as lower alkoxycarbonyl, aminocarbonyl, N-lower alkylaminocarbonyl, N,N-di-lower alkylamino-carbonyl, cyano or amidino. Conversely, carboxylic acid derivatives can also be converted into free carboxylic acids, for example by hydrolysis.

Compounds of formula I wherein R_2 is hydrogen can be converted by reaction with a halogenating agent, for example a N-halosuccinimide, into compounds of formula I wherein R_2 is halogen.

For example, hydroxy groups can be esterified with organic or inorganic acids or etherified with alcohols or organic halides or they can be removed by reduction.

If any of the intermediates contain troublesome reactive groups, for example carboxy, hydroxy, mercapto or amino groups, those groups can be protected temporarily by readily removable protecting groups. The choice of suitable protecting groups, their introduction and their removal are known *per se* and are described, for example, in J.F.W. McOmie, *Protective Groups in Organic Chemistry*, Plenum Press, London, New York 1973 and, for example, in T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York *et al.*, 1991, or also in P.J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, New York 1994.

Salts of compounds I can be prepared in a manner known *per se*. For example, acid addition salts of compounds I are obtained by treatment with a suitable acid or a suitable ion exchange reagent and salts with bases by treatment with a suitable base or a suitable ion exchange reagent. Salts of compounds of formula I can be converted into the free compounds I in customary manner: acid addition salts, for example, by treatment with a

suitable basic agent or a suitable ion exchange reagent and salts with bases, for example, by treatment with a suitable acid or a suitable ion exchange reagent.

Salts of compounds I can be converted in a manner known *per se* into other salts of compounds I: acid addition salts can be converted, for example, into other acid addition salts, for example by treatment of a salt of an inorganic acid, such as a hydrochloride, with a suitable metal salt, such as a sodium, barium or silver salt, of an acid, for example with silver acetate, in a suitable solvent in which an inorganic salt that forms, for example silver chloride, is insoluble and thus precipitates from the reaction mixture.

Depending upon the procedure and reaction conditions, compounds I having salt-forming properties can be obtained in free form or in the form of salts.

Owing to the close relationship between the compound I in free form and in the form of its salts, hereinbefore and hereinafter any reference to the free compound I or its salts should be understood as including also the corresponding salts or the free compound I, respectively, as appropriate and expedient.

The compounds I, including the salts of salt-forming compounds, can also be obtained in the form of their hydrates and/or may include other solvents, for example solvents that may have been used for the crystallisation of compounds in solid form.

Depending upon the starting materials and procedures chosen, the compounds I and their salts may be in the form of one of the possible isomers or in the form of a mixture thereof. There are obtainable as pure isomers, for example, pure diastereoisomers. Accordingly, isomeric mixtures may be in the form of, for example, diastereoisomeric mixtures. Isomeric mixtures of compounds I in free form or in salt form obtainable in accordance with the process or by another method can be separated into their components in customary manner, for example on the basis of the physico-chemical differences between the constituents in known manner by fractional crystallisation, distillation and/or chromatography. Advantageously, the more active isomer is isolated.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining

steps are carried out or a starting material is used in the form of a derivative or salt or, especially, is formed under the reaction conditions.

In the process of the present invention it is preferable to use those starting materials and intermediates, in each case in free form or in salt form, which result in the compounds I described at the beginning as being especially valuable or the salts thereof. The invention relates also to novel starting materials and intermediates, in each case in free form or in salt form, for the preparation of compounds I or the salts thereof, to the use thereof and to processes for their preparation, the variable R being as defined for compounds I.

The invention relates also to the use of compounds I and their pharmaceutically acceptable salts in the treatment of allergic conditions and diseases, preferably in the form of pharmaceutically acceptable preparations, especially in a method for the therapeutic treatment of the animal or human body, and to such a method of treatment.

The invention relates also to pharmaceutical compositions comprising as active ingredient a compound I or a pharmaceutically acceptable salt thereof, and to processes for their preparation. Those pharmaceutical compositions are, for example, for enteral, such as especially oral, also rectal, administration, for parenteral administration and for local administration to warm-blooded animals, especially humans, the compositions comprising the pharmacological active ingredient on its own or together with customary pharmaceutical excipients. The pharmaceutical compositions comprise (in percent by weight) for example from approximately 0.001 % to 100 %, preferably from approximately 0.1 % to approximately 50 %, active ingredient.

Pharmaceutical compositions for enteral or parenteral administration are, for example, those in unit dose forms, such as dragées, tablets, capsules or suppositories, and also ampoules. They are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising procedures. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture or granules, if desired or necessary after the addition of appropriate excipients, into tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, *inter alia*, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Further orally administrable pharmaceutical compositions are hard gelatin capsules, and also soft, sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The hard gelatin capsules may comprise the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also have been added.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base material. Suitable suppository base materials are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. It is also possible to use gelatin rectal capsules which comprise a combination of the active ingredient with a base material. Suitable base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

For parenteral administration there are suitable, especially, aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, and also suspensions of the active ingredient, such as corresponding oily injection suspensions, there being used suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions which comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and optionally also stabilisers.

Pharmaceutical compositions for local administration are, for example for topical treatment of the skin, lotions, creams and ointments, i.e. liquid or semi-solid oil-in-water or water-in-oil emulsions, fatty ointments, which are anhydrous, pastes, i.e. creams and ointments having secretion-absorbing powder constituents, gels, which are aqueous, of low water content or anhydrous and consist of swellable, gel-forming materials, foams, i.e. liquid oil-in-water emulsions in aerosol form which are administered from pressurised containers, and tinctures having an aqueous-ethanolic base and may comprise other customary pharmaceutical excipients, such as preservatives. The pharmaceutical compositions for local administration are prepared in a manner known *per se* by mixing the active ingredient with the pharmaceutical excipients, for example by dissolving or suspending the active ingredient in the base or in a portion thereof, if necessary. In order to prepare emulsions in which the active ingredient is dissolved in one of the liquid phases, the active ingredient is normally dissolved therein prior to emulsification; in order to prepare suspensions in which the active ingredient is suspended in the emulsion, the active ingredient is mixed with a portion of the base after emulsification and then added to the remainder of the formulation.

The dosage of the active ingredient can depend upon various factors, such as the effectiveness and duration of action of the active ingredient, the severity of the disease to be treated and of its symptoms, the mode of administration, the species of warm-blooded animal, and the sex, age, weight and/or individual condition of the warm-blooded animal. In a normal case, the, for example oral, daily dose for a warm-blooded animal weighing approximately 75 kg is estimated to be from approximately 1 mg to approximately 1000 mg, especially from approximately 5 mg to approximately 200 mg. It can be administered, for example, as a single dose or in several part doses of, for example, from 10 to 100 mg.

The following Examples are intended to illustrate the invention described hereinbefore, but without limiting the invention thereto. (Hereinbefore and hereinafter, unless otherwise indicated the meanings of the following abbreviations are: M.p.: = melting point; $CDCl_3$ = deuterochloroform; DMSO-d_6 = hexadeuterodimethyl sulfoxide; CD_3OD = deuteromethanol; $C_2D_2Cl_4$ = deuterotetrachloroethane).

Example 1: 5-Isopropyl-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

0.252 g of 4-chloro-5-isopropyl-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidine is stirred in a bomb tube with 15 ml of ammonia at 130°C for 24 hours. The ammonia is evaporated off and the residue is purified by flash chromatography (methylene chloride/methanol 10:0.4). M.p.: 96-98°C. ^{1}H-NMR ($CDCl_3$, ppm): 8.50 (s, 1H), 8.0 (d, 2H), 7.65 (s, 1H), 7.45 (m, 2H), 7.25 (m, 1H), 5.1 (s, 2H), 4.7 (qq, 1H), 1.68 (d, 6H).

a) (3-Nitrilo-2-phenyl-propenylamino)-acetic acid ethyl ester: 2.50 g of glycine ethyl ester hydrochloride are suspended in 200 ml of toluene, and 2.50 ml of triethylamine, 2.60 g of α-formyl-phenylacetonitrile and 0.050 g of toluenesulfonic acid are added and stirring is carried out under reflux using a water separator for 1.5 hours. The reaction mixture is cooled to room temperature and filtered. The filtrate is concentrated by evaporation using a rotary evaporator and the residue is dried under a high vacuum. ^{1}H-NMR ($CDCl_3$, ppm): 7.42-7.32 (m, 4H), 7.18 (m, 1H), 7.12 (s, 1H), 5.45 (m (broad), 1H), 4.3 (q, 2H), 4.08 (d, 2H), 1.30 (t, 3H).

α-Formyl-phenylacetonitrile *[CAS Reg.No.:5841-70-3]* is prepared according to J.D. Albright *et al.* US 79-34060.

b) 3-Amino-4-phenyl-*1H*-pyrrole-2-carboxylic acid ethyl ester: 0.430 g of sodium is dissolved in 20 ml of ethanol (absolute) and then 4.00 g of (3-nitrilo-2-phenyl-propenylamino)-acetic acid ethyl ester are added. The reaction mixture is stirred at room temperature for 48 hours and then poured into 300 ml of water. The suspension is filtered and the solid is dissolved in methylene chloride, the organic phase is extracted with saturated sodium chloride solution and dried over sodium sulfate, and the solvent is removed using a rotary evaporator. The

residue is purified by flash chromatography (diethyl ether/petroleum ether 1:1). ^{1}H-NMR ($CDCl_3$, ppm): 8.30 (s (broad),1H), 7.50-7.30 (m, 5H), 6.85 (d, 1H), 4.6 (s (broad), 2H), 4.3 (q, 2H), 1.38 (t, 3H).

c) 3-(Dimethylamino-methyleneamino)-4-phenyl-*1H*-pyrrole-2-carboxylic acid ethyl ester: 2.10 g of 3-amino-4-phenyl-*1H*-pyrrole-2-carboxylic acid ethyl ester and 12.0 ml of dimethylformamide dineopentyl acetal are dissolved in 12.0 ml of chloroform and stirring is carried out at 70°C for 4 days. The reaction mixture is concentrated by evaporation using a rotary evaporator and the residue is purified by flash chromatography (diethyl ether/-petroleum ether 3:1). ^{1}H-NMR ($CDCl_3$, ppm): 8.70 (s (broad), 1H), 7.75 (d, 2H), 7.52 (s, 1H), 7.45 (m, 2H), 7.18 (m, 1H), 7.05 (d, 1H), 4.30 (q, 2H), 3.08 (s (broad), 6H), 1.35 (t, 3H).

d) 7-Phenyl-3,5-dihydro-pyrrolo[3,2-d]pyrimidin-4-one: 1.00 g of 3-(dimethylamino-methyleneamino)-4-phenyl-*1H*-pyrrole-2-carboxylic acid ethyl ester is dissolved in 100 ml of ammonia/methanol and stirring is carried out at 45°C in a bomb tube. Cooling to room temperature is then carried out and the suspension is filtered. ^{1}H-NMR (DMSO-d_6, ppm): 12.2 (s (broad), 2H), 8.12 (d, 2H), 7.90 (d, 2H), 7.38 (m, 2H), 7.19 (m, 1H).

e) 4-Chloro-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidine: 1.00 g of 7-phenyl-3,5-dihydro-pyrrolo-[3,2-d]pyrimidin-4-one is stirred in 20 ml of phosphoryl chloride at 120°C for 15 hours. Phosphoryl chloride is removed using a rotary evaporator and the residue is dissolved in water and rendered alkaline with 25 % ammonia. The suspension is filtered and the product is dried. ^{1}H-NMR (DMSO-d_6, ppm): 12.7 (s, 1H), 8.8 (s, 1H), 8.55 (d, 1H), 8.25 (d, 2H), 7.45 (m, 2H), 7.30 (t, 1H).

f) 4-Chloro-5-isopropyl-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidine: 0.250 g of 4-chloro-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidine is dissolved in 5 ml of dimethylformamide, and 0.300 g of potassium carbonate and 0.332 g of 18-crown-6 ether are added. The reaction mixture is stirred at 70°C for 10 minutes, then 0.200 ml of 2-bromopropane is added and stirring is again carried out at 70°C for 5 hours. The suspension is poured into water and extracted with ethyl acetate. The organic phase is separated and dried over sodium sulfate, and the solvent is removed using a rotary evaporator. The residue is purified by flash chromato-

graphy (petroleum ether/ethyl acetate 6:1). ^{1}H-NMR ($CDCl_3$, ppm): 8.8 (s, 1H), 8.08 (d, 2H), 7.92 (s, 1H), 7.50 (m, 2H), 7.40 (m, 1H), 5.10 (m, 1H), 1.70 (d, 6H).

The following Examples are prepared analogously using 4-chloro-7-phenyl-*5H*-pyrrolo-[3,2-d]pyrimidine and the appropriate bromides as starting materials:

Example 2: 5-Cyclopentyl-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine
M.p.: 211-212°C. ^{1}H-NMR ($CDCl_3$, ppm): 8.5 (s, 1H), 8.05 (m, 2H), 7.45 (m, 3H), 7.2 (s,1H), 5.1 (s, 2H), 4.95 (m, 1H), 2.4-2.2 (m, 8H).

Example 3: 5-(2-Methoxy-ethoxymethyl)-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine
M.p.: 161-162°C. ^{1}H-NMR ($CDCl_3$, ppm): 8.5 (s, 1H), 8.0 (m, 2H), 7.45 (m, 3H), 7.2 (s, 1H), 5.8 (s, 2H), 5.6 (s, 2H), 3.7 (m, 2H), 3.59 (m, 2H), 3.4 (s, 3H).

Example 4: 5-[2-(2-Methoxy-ethoxy)-ethyl]-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine
M.p.: 150-151°C. ^{1}H-NMR ($CDCl_3$, ppm): 8.5 (s, 1H), 8.05 (m, 2H), 7.45 (m, 3H), 7.2 (s, 1H), 5.8 (s, 2H), 4.55 (t, 2H), 3.95 (t, 2H), 3.62 (m, 2H), 3.48 (m, 2H), 3.3 (s, 3H).

Example 5: (*4R/2S*) 4-(4-Amino-7-phenyl-pyrrolo[3,2-d]pyrimidin-5-yl)-2-carbamoyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester
^{1}H-NMR ($CDCl_3$, ppm): 8.5 (s, 1H), 7.98 (d, 2H), 7.5 (m, 3H), 7.22 (s, 1H), 6.0 (s, 2H), 5.50 (m, 1H), 4.98 (d, 1H), 4.12 (t, 1H), 3.90 (t, 1H), 2.99 (m, 1H), 2.1 (m, 1H), 1.1 (s, 9H).

Example 6: (*4R/2R*) 4-(4-Amino-7-phenyl-pyrrolo[3,2-d]pyrimidin-5-yl)-2-carbamoyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester
^{1}H-NMR ($C_2D_2Cl_4$, ppm): 8.5 (s, 1H), 7.98 (d, 2H), 7.5 (m, 3H), 7.22 (s, 1H), 6.0 (s, 2H), 5.50 (m, 1H), 4.98 (d, 1H), 4.12 (t, 1H), 3.90 (t, 1H), 2.99 (m, 1H), 2.1 (m, 1H), 1.1 (s, 9H).

Example 7: 5,7-Diphenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine
0.200 g of 4-chloro-5,7-diphenyl-*5H*-pyrrolo[3,2-d]pyrimidine is stirred in a bomb tube with 15 ml of ammonia at 40°C for 7 days. Unreacted ammonia is evaporated off and the residue is recrystallised from ethanol. M.p.:199-201°C. ^{1}H-NMR ($CDCl_3$, ppm): 8.55 (s, 1H), 8.08 (d, 2H), 7.65-7.4 (m, 8H), 7.27 (s, 1H), 4.80 (s, 2H).

a) [(3-Nitrilo-2-phenyl-propenyl)-phenyl-amino]-acetic acid ethyl ester: 4.48 g of phenyl-amino-acetic acid ethyl ester, 3.60 g of α-formyl-phenylacetonitrile and 0.100 g of toluenesulfonic acid are dissolved in 200 ml of toluene and stirred under reflux using a water separator for 1.5 hours. The reaction mixture is cooled to room temperature and concentrated by evaporation using a rotary evaporator, and the residue is dried under a high vacuum. ^{1}H-NMR ($CDCl_3$, ppm): 7.40-7.20 (m, 11H), 4.88 (s, 2H), 4.30 (q, 2H), 1.35 (t, 3H).

α-Formyl-phenylacetonitrile *[CAS Reg.No.:5841-70-3]* is prepared according to J.D. Albright *et al. US 79-34060.*

Phenylamino-acetic acid ethyl ester *[CAS Reg.No.: 2216-92-4]* is prepared according to W.K. Anderson *et al., J. Med. Chem.* 1989, **32**, page 119.

b) 3-Amino-1,4-diphenyl-*1H*-pyrrolo-2-carboxylic acid ethyl ester: 0.115 g of sodium is dissolved in 5 ml of absolute ethanol, and 1.39 g of [(3-nitrilo-2-phenyl-propenyl)-phenyl-amino]-acetic acid ethyl ester are added, and the reaction mixture is subsequently stirred at room temperature for 1 hour. It is then poured into water and extracted with ethyl acetate. The organic phase is separated and dried over sodium sulfate, and the solvent is removed using a rotary evaporator. The residue is purified by flash chromatography (petroleum ether/diethyl ether 2:1). ^{1}H-NMR ($CDCl_3$, ppm): 7.52-7.22 (m, 10H), 6.88 (s, 1H), 4.85 (s, 2H), 4.12 (q, 2H), 1.1 (t, 3H).

c) 3-(Dimethylamino-methyleneamino)-4-phenyl-*1H*-pyrrolo-2-carboxylic acid ethyl ester: 2.10 g of 3-amino-1,4-diphenyl-*1H*-pyrrolo-2-carboxylic acid ethyl ester are dissolved in 7 ml of chloroform, and 5.97 ml of dimethylformamide dineopentyl acetal are added. The reaction mixture is stirred at 70°C for 5 days. It is then concentrated by evaporation using a rotary evaporator and the residue is solidified with petroleum ether. ^{1}H-NMR ($CDCl_3$, ppm): 7.72 (d, 2H), 7.51 (s, 1H), 7.42-7.1 (m, 8H), 7.05 (s, 1H), 4.05 (q, 2H), 3.05 (s (broad), 6H), 1.05 (t, 3H).

d) 7,5-Diphenyl-3,5-dihydro-pyrrolo[3,2-d]pyrimidin-4-one: A solution of 0.750 g of 3-(dimethylamino-methyleneamino)-4-phenyl-*1H*-pyrrolo-2-carboxylic acid ethyl ester in ammonia/methanol is stirred at room temperature for 3 days. Ammonia/methanol are removed using a rotary evaporator and the product is solidified with diethyl ether. ^{1}H-NMR ($CDCl_3$, ppm): 11.7 (s, 1H), 7.98 (d, 2H), 7.8 (s, 1H), 7.62 (s, 1H), 7.58-7.32 (m, 8H).

e) 4-Chloro-5,7-diphenyl-*5H*-pyrrolo[3,2-d]pyrimidine: 0.440 g of 7,5-diphenyl-3,5-dihydro-pyrrolo[3,2-d]pyrimidin-4-one is stirred in 1 ml of phosphoryl chloride at 115°C. Phosphoryl chloride is removed using a rotary evaporator and the product is solidified with petroleum ether. ^{1}H-NMR (CD_3OD, ppm): 8.9 (s, 1H), 8.5 (s, 1H), 7.95 (d, 2H), 7.60-7.38 (m, 8H).

The following Examples are prepared analogously to Example 7 using the variously substituted phenylaminoacetic acid ethyl ester or benzylaminoacetic acid ethyl ester and the appropriate α-formyl-acetonitrile derivative as starting materials.

Example 8: 5-Benzyl-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine
^{1}H-NMR ($CDCl_3$, ppm): 8.48 (s, 1H), 8.02 (d, 2H), 7.60-7.10 (m, 9H), 5.02 (s, 2H), 4.70 (s (broad), 2H).

Example 9: 5-(4-Methoxy-phenyl)-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine
M.p.: 240-244°C.

Example 10: 5-(3-Methoxy-phenyl)-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 11: 4-(4-Amino-7-phenyl-pyrrolo[3,2-d]pyrimidin-5-yl)-phenol
^{1}H-NMR (DMSO-d_6, ppm): 9.98 (s, 1H), 8.29 (s, 1H), 8.22 (d, 2H), 8.10 (s, 1H), 7.40 (m, 4H), 7.20 (m, 1H), 6.92 (d, 2H), 5.75 (s (broad), 2H).

Example 12: 3-(4-Amino-7-phenyl-pyrrolo[3,2-d]pyrimidin-5-yl)-phenol

Example 13: 7-[4-(2-Benzyloxy-ethoxy)-phenyl]-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

^{1}H-NMR ($CDCl_3$, ppm): 8.55 (s, 1H), 8.00 (d, 2H), 7.68-7.20 (m, 11H), 7.03 (d, 2H), 4.78 (s, 2H), 4.75 (s, 2H), 4.22 (t, 2H), 3.89 (t, 2H). M.p.: 139-141°C.

Example 14: 2-[4-(4-Amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-phenoxy]-ethanol

^{1}H-NMR (DMSO-d_6, ppm): 8.32 (s, 1H), 8.15 (m, 3H), 7.60 (m, 6H), 7.0 (d, 2H), 6.8 (s, 2H), 4.89 (t, 1H), 4.0 (t, 2H), 3.72 (m, 2H). M.p.: 190-192°C.

Example 15: 7-[4-(2-Imidazol-1-yl-ethoxy)-phenyl]-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-yl-amine

^{1}H-NMR ($CDCl_3$, ppm): 8.52 (s, 1H), 7.99 (d, 2H), 7.65 (m, 7H), 7.28 (s, 1H), 7.09 (m, 2H), 6.98 (d, 2H), 4.70 (s, 2H), 4.40 (t, 2H), 4.28 (t, 2H).

Example 16: 7-Cyclohexen-1-enyl-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

The title compound is obtained from 1.08 g of 7-cyclohex-1-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ol in a manner analogous to that described in Examples 1 and 1e), after recrystallisation from hexane/ethyl acetate. ^{1}H-NMR ($CDCl_3$, ppm): 8.55 (br. s, 1H), 7.44 (m, 1H), 7.29 (m, 1H), 7.15 (m, 1H), 7.05-6.95 (m, 2H), 6.93 (s, 1H), 4.78 (br. s, 2H), 3.87 (s, 3H), 2.45 (m, 2H), 2.32 (m, 2H), 1.81 (m, 2H), 1.71 (m, 2H). FAB-MS: 321 $[M+H]^+$.

a) Sodium 2-cyclohex-1-enyl-3-oxido-acrylonitrile: 10.3 g of sodium hydride (80 % dispersion in oil) are washed twice with absolute tetrahydrofuran and then suspended in 1.2 l of tetrahydrofuran. With stirring at room temperature, 83 ml of ethyl formate are added thereto and then a solution of 25 ml of (1-cyclohex-1-enyl)acetonitrile in 50 ml of tetrahydrofuran is added dropwise over 10 minutes. The reaction mixture is heated to 55-60°C and stirred until no further gas evolution is observed (approx. 2 hours). The viscous slurry is filtered off with suction, washed with tetrahydrofuran and dried overnight at 45°C under a high vacuum. The crude title compound is obtained in the form of a beige solid. ^{1}H-NMR (DMSO-D_6, ppm): 8.42 (s, 1H), 4.03 (m, 1H), 2.06 (m, 2H), 1.99 (m, 2H), 1.6-1.45 (m, 4H).

b) [(3-Nitrilo-2-(cyclohex-1-enyl)-propenyl)-(3-methoxyphenyl)amino]-acetic acid ethyl ester: 7.3 ml of 4M hydrogen chloride in dioxane are added at room temperature, with stirring, to a

mixture of 5.0 g of the sodium salt of 2-cyclohex-1-enyl-3-hydroxy-acrylonitrile in 50 ml of toluene. After 5 minutes, 6.1 g of N-(3-methoxyphenyl)glycine ethyl ester and a small amount of *p*-toluenesulfonic acid hydrate are added and the suspension is heated under reflux using a water separator. After 1 hour, the reaction mixture is left to cool, the undissolved residue is removed by filtration and the filtrate is concentrated. The oily residue is pre-purified by flash chromatography (hexane/ethyl acetate 10:1). Unreacted N-(3-methoxyphenyl)glycine ethyl ester is then substantially removed from the resulting crude product by bulb tube distillation (170-180°C/0.06 mbar). The crude title compound is obtained in the form of a coloured oil. ^{1}H-NMR ($CDCl_3$, ppm): 7.28 (m, 1H), 6.96 (s, 1H), 6.75-6.6 (m, 3H), 5.98 (m, 1H), 4.79 (s, 2H), 4.28 (q, J=7Hz, 2H), 3.81 (s, 3H), 2.2-2.1 (m, 4H), 1.71 (m, 2H), 1.61 (m, 2H), 1.31 (t, J=7Hz, 3H).

c) 3-Amino-1-(3-methoxyphenyl)-4-(cyclohex-1-enyl)-*1H*-pyrrole-2-carboxylic acid ethyl ester: The title compound is obtained from 2.18 g of [(3-nitrilo-2-(cyclohex-1-enyl)-propenyl)-(3-methoxyphenyl)amino]-acetic acid ethyl ester in a manner analogous to that described in Example 1b). ^{1}H-NMR ($CDCl_3$, ppm): 7.26 (m, 1H), 6.9-6.75 (m, 3H), 6.68 (s, 1H), 5.96 (m, 1H), 4.86 (br. s, 2H), 4.12 (q, J=7Hz, 2H), 3.81 (s, 3H), 2.3-2.15 (m, 4H), 1.74 (m, 2H), 1.66 (m, 2H), 1.07 (t, J=7Hz, 3H).

d) 7-Cyclohex-1-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ol: The title compound is obtained from 2.18 g of 3-amino-1-(3-methoxyphenyl)-4-(cyclohex-1-enyl)-*1H*-pyrrole-2-carboxylic acid ethyl ester in a manner analogous to that described in Examples 1c) and 1d). ^{1}H-NMR (DMSO-D_6, ppm): 12.1 (s, 1H), 7.90 (m, 1H), 7.56 (s, 1H), 7.35 (m, 1H), 7.1-6.9 (m, 4H), 3.78 (s, 3H), 2.39 (m, 2H), 2.18 (m, 2H), 1.70 (m, 2H), 1.62 (m, 2H). FAB-MS: 322 $[M+H]^+$.

Example 17: 7-Cyclohexyl-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine
A solution of 0.22 g of 7-cyclohex-1-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine in 10 ml of methanol is hydrogenated in the presence of 0.025 g of Pd/C (10 %) at room temperature under normal pressure for 3 days. The reaction mixture is filtered over Celite 545 and the crude product obtained after concentration of the filtrate is purified by flash chromatography (methylene chloride/methanol 97:3). ^{1}H-NMR (CD_3OD, ppm): 8.20 (s,

1H), 7.47 (m, 1H), 7.35 (s, 1H), 7.08 (m, 1H), 7.05-6.95 (m, 2H), 3.86 (s, 3H), 2.96 (m, 1H), 2.15-2.05 (m, 2H), 1.95-1.7 (m, 3H), 1.6-1.25 (m, 5H). FAB-MS: 322 M^+, 321 $[M-H]^+$.

Example 18: 7-Cyclohexen-1-enyl-5-(3-hydroxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

0.27 ml of boron tribromide is added in portions in the course of 15 minutes at 0-5°C to a solution of 0.30 g of 7-cyclohex-1-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine in 10 ml of methylene chloride and, after 2.5 hours, a further 0.27 ml of boron tribromide is added. Stirring is then carried out for a further hour, 1.5 ml of water are then added dropwise and the mixture is stirred at 0-5°C for 30 minutes. The crude product obtained after customary working-up is purified by flash chromatography (methylene chloride/methanol 95:5). ^{1}H-NMR (DMSO-D_6, ppm): 10.0 (s, 1H), 8.24 (s, 1H), 7.55 (s, 1H), 7.36 (m, 1H), 7.16 (m, 1H), 6.89 (m, 2H), 6.80 (m, 1H), 5.80 (br. s, 2H), 2.39 (m, 2H), 2.20 (m, 2H), 1.72 (m, 2H), 1.52 (m, 2H).

Example 19: 5-Phenyl-7-(pyridin-3-yl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

A solution of 0.25 g of 5-phenyl-7-(pyridin-3-yl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ol in 2 ml of phosphoryl chloride is stirred at 120°C for 2 hours. The reaction mixture is concentrated using a rotary evaporator and the residue is dried under a high vacuum. The crude product so obtained is stirred in 15 ml of liquid ammonia at 130°C in an autoclave for 24 hours. After the ammonia has been evaporated off, the solid residue is taken up in methylene chloride/-methanol 2:1 and filtered, and the residue obtained after concentration of the filtrate is purified by flash chromatography (methylene chloride/methanol 95:5). The title compound is obtained. ^{1}H-NMR ($CDCl_3$, ppm): 9.11 (br. s, 1H), 8.65-8.5 (m, 3H), 7.69 (s, 1H), 7.65-7.5 (m, 5H), 7.40 (m, 1H), 4.83 (br. s, 2H).

a) [(3-Nitrilo-2-(pyridin-3-yl)-propenyl)-phenylamino]-acetic acid ethyl ester: A mixture of 1.0 g of 3-oxo-2-(pyridin-3-yl)-propionitrile (prepared according to M. Cariou, *Bull. Soc. Chim. France* (1979), **11-12**, 651-656), 1.12 g of phenylamino-acetic acid ethyl ester and a catalytic amount of *p*-toluenesulfonic acid hydrate in 50 ml of toluene and 7 ml of dimethyl sulfoxide is stirred under reflux using a water separator for 3 hours. The reaction mixture is filtered and the filtrate is then washed with saturated sodium carbonate solution and brine, dried over magnesium sulfate and concentrated. The residue is purified by means of flash

chromatography (hexane/ethyl acetate 2:1). ^{1}H-NMR ($CDCl_3$, ppm): 8.63 (s, 1H), 8.44 (m, 1H), 7.71 (m, 1H), 7.42 (m, 2H), 7.35-7.2 (m, 5H), 4.86 (s, 2H), 4.32 (q, 2H), 1.33 (t, 3H).

b) 3-Amino-1-phenyl-4-(pyridin-3-yl)-*1H*-pyrrole-2-carboxylic acid ethyl ester: 0.38 g of [(3-nitrilo-2-(pyridin-3-yl)-propenyl)-phenylamino]-acetic acid ethyl ester, dissolved in 8 ml of absolute ethanol, is added to a solution of 32 mg of sodium in 15 ml of absolute EtOH. The reaction mixture is stirred at room temperature for 60 minutes and then concentrated using a rotary evaporator, and the residue is taken up in 40 ml of ethyl acetate. The organic phase is washed with saturated sodium carbonate solution and brine, dried over magnesium sulfate and concentrated. ^{1}H-NMR ($CDCl_3$, ppm): 8.77 (m, 1H), 8.52 (m, 1H), 7.84 (m, 1H), 7.5-7.25 (m, 6H), 6.90 (s, 1H), 4.33 (br s, 2H), 4.14 (q, 2H), 1.06 (t, 3H).

c) 3-(Dimethylamino-methyleneamino)-1-phenyl-4-(pyridin-3-yl)-*1H*-pyrrole-2-carboxylic acid ethyl ester: 1.64 ml of N,N-dimethylformamide dineopentyl acetal are added to a solution of 0.58 g of 3-amino-1-phenyl-4-(pyridin-3-yl)-*1H*-pyrrole-2-carboxylic acid ethyl ester in 5 ml of chloroform and the mixture is stirred at 70°C for 4 days. It is concentrated using a rotary evaporator and the residue is purified by flash chromatography (hexane/ethyl acetate 1:2). ^{1}H-NMR ($CDCl_3$, ppm): 8.98 (s, 1H), 8.41 (m, 1H), 8.09 (m, 1H), 7.58 (s, 1H), 7.45-7.2 (m, 6H), 7.10 (s, 1H), 4.13 (q, 2H), 3.09 (br s, 3H), 3.03 (br s, 3H), 1.02 (t, 3H).

d) 5-Phenyl-7-(pyridin-3-yl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ol: A mixture of 0.66 g of 3-(dimethylamino-methyleneamino)-1-phenyl-4-(pyridin-3-yl)-*1H*-pyrrole-2-carboxylic acid ethyl ester and 40 ml of saturated methanolic ammonia solution is stirred in a bomb tube at 40-45°C for 65 hours. The whitish suspension is filtered with suction and the residue is washed with methanol and dried at 50°C under a high vacuum. ^{1}H-NMR (DMSO-D_6, ppm): 8.20 (s, 1H), 7.65-7.5 (m, 2H), 7.08 (m, 1H), 6.84 (m, 1H), 6.7-6.6 (m, 6H), 6.49 (s, 1H).

Example 20: 4-[4-Amino-7-[4-(2-imidazol-1-yl-ethoxy)-phenyl]-pyrrolo[3,2-d]pyrimidin-5-yl]-phenol

Example 21: 3-[4-Amino-7-[4-(2-imidazol-1-yl-ethoxy)-phenyl]-pyrrolo[3,2-d]pyrimidin-5-yl]-phenol

Example 22: 7-[4-(2-Imidazol-1-yl-ethoxy)-phenyl]-5-(4-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]-pyrimidin-4-ylamine

Example 23: 7-[4-(2-Imidazol-1-yl-ethoxy)-phenyl]-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]-pyrimidin-4-ylamine

^{1}H-NMR (CD_3OD, ppm): 8.28 (s, 1H), 7.85 (d, 2H), 7.75 (d, 2H), 7.50 (t, 1H), 7.25 (s, 1H), 7.12 - 6.90 (m, 6H), 4.45 (t, 2H), 4.28 (t, 2H), 3.87 (s, 3H).

Example 24: 7-[4-(2-Amino-ethoxy)-phenyl]-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 25: 4-{4-Amino-7-[4-(2-amino-ethoxy)-phenyl]-pyrrolo[3,2-d]pyrimidin-5-yl}-phenol

Example 26: 3-{4-Amino-7-[4-(2-amino-ethoxy)-phenyl]-pyrrolo[3,2-d]pyrimidin-5-yl}-phenol

Example 27: 7-[4-(2-Amino-ethoxy)-phenyl]-5-(4-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 28: 7-[4-(2-Amino-ethoxy)-phenyl]-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

^{1}H-NMR (DMSO-d_6, ppm): 8.30 (s, 1H), 8.10 (m, 3H), 7.50 (t, 1H), 7.18 - 6.97 (m, 5H), 5.8 (s, 2H), 3.98 (t, 2H), 3.85 (s, 3H), 2.90 (t, 2H).

Example 29: 2-{2-[4-(4-Amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-phenoxy]-ethyl-amino}-ethanol

Example 30: 4-{4-Amino-7-{4-[2-(2-hydroxy-ethylamino)-ethoxy]-phenyl}-pyrrolo[3,2-d]-pyrimidin-5-yl-phenol

Example 31: 3-{4-Amino-7-{4-[2-(2-hydroxy-ethylamino)-ethoxy]-phenyl}-pyrrolo[3,2-d]-pyrimidin-5-yl-phenol

^{1}H-NMR (DMSO-d_6, ppm): 8.32 (s, 1H), 8.20 - 8.08 (m, 3H), 7.40 (t, 1H), 7.00 - 6.80 (m, 5H), 5.80 (s, 2H), 4.50 (s (broad), 1H), 4.03 (m, 2H), 3.50 (m, 2H), 2.90 (m, 2H), 2.65 (m, 2H).

Example 32: 2-2-{4-[4-Amino-5-(4-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethylamino)-ethanol

Example 33: 2-2-{4-[4-Amino-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethylamino)-ethanol
^{1}H-NMR (DMSO-d_6, ppm): 8.30 (s, 1H), 8.12 (m, 3H), 7.50 (t, 1H), 7.19 - 6.95 (m, 5H), 5.90 (s, 2H), 4.55 (s, 1H), 4.05 (t, 2H), 3.85 (s, 3H), 3.5 (m, 2H), 2.92 (m, 2H), 2.70 (m, 2H).

Example 34: 7-Cyclohexen-1-enyl-5-(3-fluoro-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 35: 7-Cyclopentyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 36: 7-Cyclopent-1-enyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 37: 7-Cyclopent-3-enyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 38: 3-(4-Amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclopentanol

Example 39: 3-(4-Amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclopent-2-enol

Example 40: 7-(3-Methoxy-cyclopentyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 41: 7-(3-Methoxy-cyclopent-1-enyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 42: [3-(4-Amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclopentyl]-methanol

Example 43: 7-(3-Methoxymethyl-cyclopentyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 44: 4-(4-Amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclopentane-1,2-diol

Example 45: 7-(3-Fluoro-cyclopentyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 46: 7-(3,4-Difluoro-cyclopentyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 47: 3-(4-Amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclohexanol

Example 48: 3-(4-Amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclohex-2-enol

Example 49: 7-(3-Methoxy-cyclohexyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 50: 7-(3-Methoxymethyl-cyclohexyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 51: 4-(4-Amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclohexanol

Example 52: 7-(4-Methoxy-cyclohexyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 53: 7-(4-Methoxymethyl-cyclohexyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 54: 5-Phenyl-7-pyrrolidin-3-yl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 55: 7-(1-Methyl-piperidin-3-yl)-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 56: 1-[3-(4-Amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-pyrrolidin-1-yl]-ethanone

Example 57: 5-Phenyl-7-piperidin-3-yl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 58: 7-(1-Methyl-piperidin-3-yl)-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 59: 1-[3-(4-Amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-piperidin-1-yl]-ethanone

Example 60: 5-Phenyl-7-piperidin-4-yl-5*H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 61: 7-(1-Methyl-piperidin-4-yl)-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 62: 1-[4-(4-Amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-piperidin-1-yl]-ethanone

Example 63: 7-(5-Methoxymethyl-pyrrolidin-3-yl)-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 64: 5-Phenyl-7-(tetrahydrofuran-3-yl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 65: 5-Phenyl-7-(tetrahydro-thiophen-3-yl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 66: 7-(1,1-Dioxo-tetrahydro-thiophen-3-yl)-5-phenyl-5*H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Example 67: 7-Cyclopent-1-enyl-5-(3-fluorophenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine
A solution of 0.07 g of sodium in 10 ml of absolute ethanol is added dropwise to a suspension of 0.81 g of N-[2-cyano-4-cyclopent-1-enyl-1-(3-fluorophenyl)-*1H*-pyrrolo-3-yl]-formamidine in 3 ml of ethanol and the mixture is stirred overnight at room temperature. It is then heated to reflux over 2 hours and, after cooling, the solvent is removed and the residue is partitioned between water and methylene chloride. Toluene is added to the combined organic phases, concentration is carried out using a rotary evaporator and the crude product is purified by means of flash chromatography on silica gel (methylene chloride/methanol 99:1). The title compound is obtained in the form of a white solid after recrystallisation from methylene chloride/hexane. ^{1}H-NMR ($CDCl_3$, ppm): 8.53 (s, 1H), 7.53 (m, 1H), 7.3-7.1 (m, 4H), 6.91 (m, 1H), 4.78 (br. s, 2H), 2.8-2.55 (m, 4H), 2.1-1.95 (m, 2H). FAB-MS: 295 $[M+H]^+$.

a) Sodium 2-cyclopent-1-enyl-3-oxido-acrylonitrile: 25.2 g of sodium hydride (80 % dispersion in oil) are washed twice with absolute tetrahydrofuran and then suspended in 1000 ml of tetrahydrofuran. 57.1 g of (1-cyclopent-1-enyl)acetonitrile are added and the mixture is heated to 50°C. After 15 minutes, 204 ml of ethyl formate are added with stirring, vigorous gas evolution commencing after a short time. After stirring at 50°C for 1 hour, the coloured suspension is filtered and the precipitate is washed with tetrahydrofuran and dried under a high vacuum. The crude title compound is obtained in the form of a beige solid.

b) 2-(Cyclopent-1-enyl)-propenyl)-3-[(3-fluorophenyl)-(2-nitriloethyl)-amino]-acrylonitrile: 32.8 ml of 4M hydrogen chloride in dioxane and a small amount of *p*-toluenesulfonic acid hydrate are added at room temperature, with stirring, to a solution of 22.5 g of the sodium salt of 2-cyclopent-1-enyl-3-hydroxy-acrylonitrile in 150 ml of toluene. A viscous slurry is obtained, to which 50 ml of toluene are added followed by heating to 80°C. 19.7 g of (3-fluorophenyl)-acetonitrile are then added and the reaction mixture is heated under reflux using a water separator. After 1 hour, the mixture is allowed to cool, the insoluble residue is removed by filtration and the filtrate is concentrated. The oily residue is pre-purified by flash chromatography on silica gel (hexane/ethyl acetate/toluene 6:1:7). Unreacted N-(3-fluorophenyl)glycine ethyl ester is then substantially removed from the resulting crude product by bulb tube distillation (160°C/0.04 mbar). The crude title compound is obtained in the form of a coloured oil.

c) 3-Amino-4-(cyclopent-1-enyl)-1-(3-fluorophenyl)-*1H*-pyrrole-2-carbonitrile: A solution of 2.45 g of 2-(cyclopent-1-enyl)-propenyl)-3-[(3-fluorophenyl)-(2-nitriloethyl)-amino]-acrylonitrile in 7 ml of ethanol is added at room temperature to a solution of 0.23 g of sodium in 20 ml of absolute ethanol and stirring is carried out for 30 minutes. The reaction mixture is concentrated, water is added to the residue and extraction is carried out with methylene chloride. The combined organic phases are dried over magnesium sulfate and concentrated, and the coloured residue is purified by means of flash chromatography on silica gel (hexane/ethyl acetate, gradient of 5:1 to 1:1). The title compound is obtained in the form of a solid. ^{1}H-NMR ($CDCl_3$, ppm): 7.42 (m, 1H), 7.24 (m, 1H), 7.14 (m, 1H), 7.04 (m, 1H), 6.82 (s, 1H), 5.87 (m, 1H), 4.03 (br, s, 2H), 2.7-2.5 (m, 4H), 2.05-1.9 (m, 2H).

d) N-[2-Cyano-4-(cyclopent-1-enyl)-1-(3-fluorophenyl)-*1H*-pyrrolo-3-yl]-formamidine: A few drops of acetic anhydride are added at room temperature, with stirring, to a mixture of 1.93 g of 3-amino-4-(cyclopent-1-enyl)-1-(3-fluorophenyl)-*1H*-pyrrole-2-carbonitrile and 20 ml of triethyl orthoformate. The reaction mixture is heated to 80°C and subsequently stirred for 3 hours. It is then concentrated and the residue is dried briefly under a high vacuum. The crude product so obtained is taken up in 40 ml of a saturated solution of ammonia in methanol, diluted with 30 ml of methylene chloride and stirred at room temperature for several days until the reaction comes to a standstill (monitoring by TLC). The reaction mixture is concentrated and the residue is purified by means of flash

chromatography on silica gel (methylene chloride/methanol 98:2). The title compound is obtained in the form of a solid. ^{1}H-NMR ($CDCl_3$, ppm): 8.53 (s, 1H), 7.55 (m, 1H), 7.35-7.1 (m, 4H), 6.92 (m, 1H), 4.76 (br. s, 2H), 2.8-2.55 (m, 4H), 2.1-1.95 (m, 2H).

Example 68: 7-Cyclopent-1-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine
The title compound is obtained from 2.96 g of 7-cyclopent-1-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ol in a manner analogous to that described in Examples 1) and 1e), after recrystallisation from hexane/ethyl acetate. ^{1}H-NMR ($CDCl_3$, ppm): 8.52 (s, 1H), 7.45 (m, 1H), 7.26 (m, 1H), 7.05-6.85 (m, 4H), 4.87 (br. s, 2H), 3.88 (s, 3H), 2.8-2.55 (2m, 4H), 2.1-1.95 (m, 2H). FAB-MS: 307 $[M+H]^+$.

a) [(3-Nitrilo-2-(cyclopent-1-enyl)-propenyl)-(3-methoxyphenyl)amino]-acetic acid ethyl ester: 62 ml of 4M hydrogen chloride in dioxane are added in portions over 3 hours to a mixture of 18.4 g of N-(3-methoxyphenyl)glycine ethyl ester, 36.8 g of the sodium salt of 2-cyclopent-1-enyl-3-hydroxy-acrylonitrile (Example 34a) and a small amount of *p*-toluenesulfonic acid in 250 ml of toluene under reflux using a water separator. The reaction mixture is then stirred for a further 30 minutes and, after cooling, the precipitate is removed by filtration and the filtrate is washed with saturated sodium hydrogen carbonate solution. The aqueous phase is back-extracted with toluene and the combined organic phases are dried over magnesium sulfate and concentrated. The majority of the unreacted N-(3-methoxyphenyl)glycine ethyl ester is removed from the resulting crude product by solid distillation under a high vacuum (0.15 mbar; bath temperature 160-180°C). Further purification of the crude product is carried out by means of flash chromatography (hexane/ethyl acetate 9:1) and, if necessary, by bulb tube distillation once more (180°C/0.08 bar). The crude title compound is obtained in the form of a coloured oil. ^{1}H-NMR ($CDCl_3$, ppm): 7.29 (m, 1H), 6.9-6.85 (m, 3H), 6.71 (s, 1H), 5.81 (m, 1H), 4.91 (br. s, 2H), 4.13 (q, J=7Hz, 2H), 3.81 (s, 3H), 2.65-2.5 (m, 4H), 2.0-1.9 (m, 2H), 1.08 (t, J=7Hz, 3H).

b) 3-Amino-1-(3-methoxyphenyl)-4-(cyclopent-1-enyl)-*1H*-pyrrole-2-carboxylic acid ethyl ester: The title compound is obtained from 6.75 g of [(3-nitrilo-2-(cyclopent-1-enyl)-propenyl)-(3-methoxyphenyl)amino]-acetic acid ethyl ester in a manner analogous to that described in Example 1b).

c) 7-Cyclopent-1-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ol: The title compound is obtained from 6.74 g of 3-amino-1-(3-methoxyphenyl)-4-(cyclopent-1-enyl)-*1H*-pyrrole-2-carboxylic acid ethyl ester in a manner analogous to that described in Examples 1c) and 1d). ^{1}H-NMR (DMSO-D_6, ppm): 12.1 (s, 1H), 7.95 (s, 1H), 7.60 (s, 1H), 7.36 (m, 1H), 7.15-6.9 (m, 3H), 6.66 (m, 1H), 3.80 (s, 3H), 2.75-2.6 (m, 2H), 2.6-2.4 (m, 2H; superimposed by solvent signal), 2.0-1.85 (m, 2H). FAB-MS: 308 $[M+H]^+$.

Example 69: 7-Cyclopent-1-enyl-5-(4-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine
The title compound is obtained in the form of a solid from 5.1 g of 7-cyclopent-1-enyl-5-(4-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ol in a manner analogous to that described in Examples 1) and 1e), after recrystallisation from methylene chloride/hexane. ^{1}H-NMR ($CDCl_3$, ppm): 8.49 (s, 1H), 7.45-6.95 (m, 5H), 6.87 (m, 1H), 4.80 (br. s, 2H), 3.89 (s, 3H), 2.8-2.5 (m, 4H), 2.1-1.95 (m, 2H). FAB-MS: 307 $[M+H]^+$.

a) [(3-Nitrilo-2-(cyclopent-1-enyl)-propenyl)-(4-methoxyphenyl)amino]-acetic acid ethyl ester: 60.0 g of the sodium salt of 2-cyclopent-1-enyl-3-hydroxy-acrylonitrile (Example 34) and a small amount of *p*-toluenesulfonic acid hydrate are added at 80°C, with stirring, to a solution of 73.3 g of N-(4-methoxyphenyl)glycine ethyl ester in 500 ml of toluene and 87.6 ml of 4M hydrogen chloride in dioxane, and the reaction mixture is heated under reflux using a water separator. After 1 hour, the reaction mixture is allowed to cool, the undissolved residue is removed by filtration and the filtrate is concentrated. The oily residue is pre-purified by flash chromatography on silica gel (hexane/ethyl acetate/toluene 6:1:7). Unreacted N-(4-methoxyphenyl)glycine ethyl ester is then substantially removed from the resulting crude product by bulb tube distillation (210°C/0.07 mbar). The title compound is obtained in the form of a solid after recrystallisation from methylene chloride/hexane. ^{1}H-NMR ($CDCl_3$, ppm): 7.2-7.1 (m, 2H), 6.95-6.85 (m, 2H), 6.75 (s, 1H), 5.75 (m, 1H), 4.66 (s, 2H), 4.27 (q, J=7Hz, 2H), 3.81 (s, 3H), 2.5-2.3 (m, 4H), 2.0-1.9 (m, 2H), 1.31 (t, J=7Hz, 3H).

b) 3-Amino-1-(4-methoxyphenyl)-4-(cyclopent-1-enyl)-*1H*-pyrrole-2-carboxylic acid ethyl ester: The title compound is obtained in the form of a solid (recrystallised from ethyl acetate/hexane) from 34.6 g of [(3-nitrilo-2-(cyclopent-1-enyl)-propenyl)-(4-methoxyphenyl)amino]-acetic acid ethyl ester in a manner analogous to that described in Example 1b). M.p. 113.5-115°C. ^{1}H-NMR ($CDCl_3$, ppm): 7.18 (m, 2H), 6.90 (m, 2H), 6.65 (s, 1H), 5.83

(m, 1H), 4.87 (br. s, 2H), 4.12 (q, J=7Hz, 2H), 3.84 (s, 3H), 2.65-2.5 (m, 4H), 2.0-1.85 (m, 2H), 1.09 (t, J=7Hz, 3H). FAB-MS: 327 $[M+H]^+$.

c) 7-Cyclopent-1-enyl-5-(4-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ol: The title compound is obtained in the form of a solid from 7.0 g of 3-amino-1-(4-methoxyphenyl)-4-(cyclopent-1-enyl)-*1H*-pyrrole-2-carboxylic acid ethyl ester in a manner analogous to that described in Examples 1c) and 1d). M.p. >253°C (decomp.). ^{1}H-NMR (DMSO-D_6, ppm): 12.1 (s, 1H), 7.91 (s, 1H), 7.49 (s, 1H), 7.40 (m, 2H), 7.00 (m, 2H), 6.63 (m, 1H), 3.81 (s, 3H), 2.75-2.6 (m, 2H), 2.6-2.4 (m, 2H; superimposed by solvent signal), 1.97-1.8 (m, 2H). FAB-MS: 308 $[M+H]^+$.

Example 70: 7-Cyclopent-1-enyl-5-(3-hydroxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine 0.47 ml of boron tribromide is added dropwise at 0-5°C, with stirring, to a suspension of 0.5 g of 7-cyclopent-1-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine in 10 ml of methylene chloride. After 45 minutes, a further 0.16 ml of boron tribromide is added and stirring is subsequently carried out for 30 minutes. 3.5 ml of water are added to the reaction mixture which is then allowed to warm slowly to room temperature and the coloured suspension is subsequently stirred for 90 minutes. The mixture is then neutralised with sodium hydroxide solution, and the resulting precipitate is filtered off and washed with a small amount of water and methylene chloride. The crude product is purified by recrystallisation from methanol. M.p. >225°C (decomp.). ^{1}H-NMR (DMSO-D_6, ppm): 10.0 (s, 1H), 8.28 (s, 1H), 7.58 (s, 1H), 7.37 (m, 1H), 6.95-6.8 (m, 3H), 6.76 (m, 1H), 5.86 (br. s, 2H), 2.75-2.6 (m, 2H), 2.6-2.4 (m, 2H; superimposed by solvent signal), 1.95-1.8 (m, 2H). FAB-MS: 293 $[M+H]^+$.

Example 71: 7-Cyclopent-1-enyl-5-(4-hydroxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine The title compound is obtained in the form of a solid from 1.0 g of 7-cyclopent-1-enyl-5-(4-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine in a manner analogous to that described in Example 70). ^{1}H-NMR (DMSO-D_6, ppm): 9.94 (s, 1H), 8.24 (s, 1H), 7.48 (s, 1H), 7.30 (m, 2H), 6.91 (m, 2H), 6.73 (m, 1H), 5.66 (br. s, 2H), 2.75-2.6 (m, 2H), 2.6-2.4 (m, 2H; superimposed by solvent signal), 1.95-1.8 (m, 2H). FAB-MS: 293 $[M+H]^+$.

Example 72: 7-Cyclopentyl-5-(4-hydroxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

A solution of 0.22 g of 7-cyclopent-1-enyl-5-(4-hydroxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine in 20 ml of methanol is hydrogenated in the presence of 0.06 g of 10 % palladium-on-carbon for 24 hours at room temperature. The crude product obtained after customary working-up is purified by flash chromatography on silica gel (methylene chloride/methanol 95:5). The title compound is obtained in the form of a solid. ^{1}H-NMR (CD_3OD, ppm): 8.16 (s, 1H), 7.3-7.25 (m, 3H), 6.9-7.0 (m, 2H), 2.25-2.1 (m, 2H), 1.9-1.6 (m, 7H). FAB-MS: 295 $[M+H]^+$.

Example 73: 7-Cyclopentyl-5-(3-hydroxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

The title compound is obtained in the form of a solid from 0.30 g of 7-cyclopent-1-enyl-5-(3-hydroxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine in a manner analogous to that described in Example 72). ^{1}H-NMR (DMSO-D_6, ppm): 9.97 (s, 1H), 8.19 (s, 1H), 7.43 (s, 1H), 7.34 (m, 1H), 6.9-6.8 (m, 2H), 6.77 (m, 1H), 5.77 (br. s, 2H), 3.19 (m, 1H), 2.1-1.95 (m, 2H), 1.85-1.55 (m, 6H). FAB-MS: 295 $[M+H]^+$.

Example 74: 7-Cyclopentyl-5-(3-fluorophenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Obtained in the form of a solid from 0.22 g of 7-cyclopent-1-enyl-5-(3-fluorophenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine in a manner analogous to that described in Example 30), after recrystallisation from methylene chloride/hexane. ^{1}H-NMR (DMSO-D_6, ppm): 8.22 (s, 1H), 7.55 (m, 1H), 7.53 (s, 1H), 7.4-7.2 (m, 3H), 5.92 (br. s, 2H), 3.20 (m, 1H), 2.1-1.95 (m, 2H), 1.85-1.55 (m, 6H). FAB-MS: 297 $[M+H]^+$.

Example 75: 7-Isopropyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

Reaction of 2.0 g of 7-isopropyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ol in 10 ml of phosphorus oxychloride at 120°C for 2 hours, working-up and further reaction in methanolic ammonia under pressure at 130°C in a manner analogous to that described in Example 19) yield the title compound in the form of a white solid after recrystallisation from 1:3 hexane/ethyl acetate. ^{1}H-NMR ($CDCl_3$, ppm): 8.43 (s, 1H), 7.45 (m, 1H), 7.21 (s, 1H), 7.05-6.9 (m, 3H), 5.28 (br. s, 2H), 3.88 (s, 3H), 3.78 (m, 1H), 1.40 (d, J=7Hz, 6H). FAB-MS: 283 $[M+H]^+$.

a) [2-Cyano-3-methyl-but-1-enyl)-(3-methoxyphenyl)amino]-acetic acid ethyl ester: A mixture of 10.0 g of isovaleronitrile and ethanolic sodium ethanolate solution (2.76 g of sodium in 33 ml of absolute ethanol) in 36 ml of toluene is stirred at 50°C and 40-50 bar pressure under a carbon monoxide atmosphere for 10 hours analogously to a known process (DE 2753322 A1). After concentration of the reaction mixture by evaporation and drying under a high vacuum, the crude sodium 2-isopropyl-3-oxido-acrylonitrile is obtained in the form of a beige solid. Without further purification, the crude product is dissolved in about 45 ml of water and adjusted to pH 6 by the addition of 1N hydrochloric acid. Extraction is then carried out with toluene, and the combined organic phases are washed with saturated sodium chloride solution, dried over magnesium sulfate and filtered. The filtrate is added to a solution, heated to 50°C, of 8.95 g of N-(3-methoxyphenyl)glycine ethyl ester in 50 ml of toluene, a catalytic amount of *p*-toluenesulfonic acid is added to the reaction mixture and heating is then carried out under reflux for 1 hour. After cooling, washing is carried out with 5 % sodium hydrogen carbonate solution and saturated sodium chloride solution, followed by drying over magnesium sulfate and concentration. Contents of N-(3-methoxyphenyl)-glycine ethyl ester contained in the crude product are substantially removed by bulb tube distillation at 220°C/5.5 mbar. Further purification by means of flash chromatography on silica gel (hexane/ethyl acetate/toluene 5:1:5) yields the title compound in the form of an oil. ^{1}H-NMR ($CDCl_3$, ppm): 7.25 (m, 1H), 6.80 (s, 1H), 6.7-6.55 (m, 3H), 4.72, (s, 2H), 4.28 (q, J=7Hz, 2H), 3.81 (s, 3H), 2.43 (m, 1H), 1.31 (t, J=7Hz, 3H), 1.17 (d, J=7Hz, 6H).

b) 3-Amino-4-isopropyl-1-(3-methoxyphenyl)-*1H*-pyrrole-2-carboxylic acid ethyl ester: The title compound is obtained from 2.46 g of [2-cyano-3-methyl-but-1-enyl)-(3-methoxyphenyl)-amino]-acetic acid ethyl ester in a manner analogous to that described in Example 1b). ^{1}H-NMR ($CDCl_3$, ppm): 7.25 (m, 1H), 6.85-6.75 (m, 3H), 6.57 (s, 1H), 4.55 (br. s, 2H), 4.14 (q, J=7Hz, 2H), 3.81 (s, 3H), 2.75 (m, 1H), 1.23 (d, J=7Hz, 6H), 1.09 (t, J=7Hz, 3H).

c) 7-Isopropyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ol: A mixture of 2.1 g of 3-amino-4-isopropyl-1-(3-methoxyphenyl)-*1H*-pyrrole-2-carboxylic acid ethyl ester and 6.05 ml of N,N-dimethylformamide dineopentyl acetal in 30 ml of chloroform is stirred under reflux at 70°C for 4 days. The reaction mixture is concentrated and dried briefly under a high vacuum, and the oily residue is purified by means of flash chromatography on silica gel (methylene chloride/methanol 95:5). Further reaction of the resulting oil in a saturated solution of ammonia in methanol at 40-45°C for 24 hours yields the title compound in the

form of a white solid. ^{1}H-NMR (CD_3OD, ppm): 8.88 (s, 1H), 7.35-7.25 (m, 2H), 7.05-6.9 (m, 3H), 3.81 (s, 3H), 3.25 (m, 1H), 1.34 (d, J=7Hz, 6H). FAB-MS: 284 $[M+H]^+$.

Example 76: 5-(3-Hydroxyphenyl)-7-isopropyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

0.5 ml of boron tribromide is added in portions over 20 minutes at 0°C to a solution of 0.5 g of 7-isopropyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine in 30 ml of methylene chloride. The resulting suspension is further stirred at 0-5°C for 2 hours and then, with ice cooling, 10 ml of water are added. The mixture is allowed to warm to room temperature and is subsequently stirred for a further hour. The reaction mixture is rendered neutral by the addition of 1N sodium hydroxide solution, after 5 minutes is filtered over a glass frit and the residue is washed with a small amount of water and methylene chloride. The crude product is recrystallised from 2:1 ethyl acetate/methanol. White solid: m.p. >273°C (decomp.). ^{1}H-NMR (CD_3OD, ppm): 8.19 (s, 1H), 7.4-7.3 (m, 2H), 6.95-6.8 (m, 3H), 3.29 (m, 1H), 1.36 (d, J=7Hz, 6H). FAB-MS: 269 $[M+H]^+$.

Example 77: 7-Cyclopent-3-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

2.1 g of 7-cyclopent-3-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ol and 10 ml of phosphorus oxychloride are stirred at 120°C for 2 hours. After concentration of the reaction mixture and drying under a high vacuum, 4-chloro-7-cyclopent-3-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidine is obtained as the crude product. ^{1}H-NMR ($CDCl_3$, ppm): 9.05 (s, 1H), 7.71 (s, 1H), 7.46 (t, J=8.5Hz, 1H), 7.13 (dd, J=2.4 and 8.5Hz, 1H), 6.98 (m, 1H), 6.93 (d, J=2.4Hz, 1H), 5.83 (m, 2H), 4.13 (m, 1H), 3.88 (s, 3H), 3.2-3.0 (m, 2H), 2.55-2.4 (m, 2H). Reaction of 4.03 g of the oil so obtained in 50 ml of liquid ammonia at 130°C for 24 hours yields the title compound in the form of a solid after recrystallisation from 1:10 methylene chloride/methanol. M.p. 175.5-176°C. ^{1}H-NMR ($CDCl_3$, ppm): 8.49 (br. s, 1H), 7.43 (m, 1H), 7.21 (s, 1H), 7.05-6.9 (m, 3H), 5.83 (m, 2H), 4.88 (br. s, 2H), 3.95-3.8 (m, 4H), 3.0-2.85 (m, 2H), 2.65-2.45 (m, 2H). FAB-MS: 307 $[M+H]^+$.

a) Toluene-4-sulfonic acid cyclopent-3-enyl-methyl ester: 145 g of *p*-toluenesulfonyl chloride, dissolved in 200 ml of pyridine, are added dropwise, with stirring at 0-5°C, to a solution of 62 g of cyclopent-3-enyl-methanol (prepared according to the method described by A. Hutchison *et al.* in *J. Heterocyclic Chem.* (1989), **26**, pages 451-452) in 400 ml of pyridine. Stirring is then carried out at 0-5°C for 16 hours, and the reaction mixture is

subsequently poured into 600 ml of ice-water and extracted with *tert*-butyl methyl ether. The combined organic phases are washed with water, 1N hydrochloric acid and saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The crude title compound is obtained in the form of an oil. ^{1}H-NMR ($CDCl_3$, ppm): 7.79 (m, 2H), 7.33 (m, 2H), 5.58 (m, 2H), 3.91 (d, J=7.5Hz, 2H), 2.61 (m, 1H), 2.5-2.35 (m, 5H; s at 2.44 ppm), 2.1-1.95 (m, 2H).

b) Cyclopent-3-enyl-acetonitrile: A mixture of 115.7 g of toluene-4-sulfonic acid cyclopent-3-enyl -methyl ester and 60 g of potassium cyanide in 800 ml of 90 % aqueous ethanol is stirred under reflux for 12 hours. After cooling, the reaction mixture is poured into 500 ml of ice-water and extracted with *tert*-butyl methyl ether, and the combined organic phases are washed with water and saturated sodium chloride solution and concentrated after drying over magnesium sulfate. The title compound is obtained in the form of a colourless liquid after distillation of the crude product. ^{1}H-NMR ($CDCl_3$, ppm): 5.64 (m, 2H), 2.65-2.5 (m, 3H), 2.33 (m, 2H), 2.7-2.0 (m, 2H).

c) [(2-Cyclopent-3-enyl-3-nitrilo-propenyl)-(3-methoxyphenyl)amino]acetic acid ethyl ester: A mixture of 20.0 g of cyclopent-3-enyl-acetonitrile and sodium ethanolate (prepared from 4.3 g of sodium in 50 ml of absolute ethanol) in 50 ml of toluene is stirred under a carbon monoxide atmosphere at 50°C and 40-50 bar pressure for 10 hours. Subsequent concentration of the reaction mixture and drying under a high vacuum yield the crude sodium 2-cyclopent-3-enyl-3-oxido-acrylonitrile in the form of a beige solid. A solution of 10.7 g of the crude product so obtained in 30 ml of water is adjusted to pH 6 with 1N hydrochloric acid and extracted twice with 100 ml of toluene. The combined organic phases are dried over magnesium sulfate, filtered and then added, at 50°C, to a solution of 7.15 g of N-(3-methoxyphenyl)glycine ethyl ester in 50 ml of toluene. After the addition of a catalytic amount of *p*-toluenesulfonic acid, the reaction mixture is stirred under reflux for 60 minutes and, after cooling, the organic phase is washed with 5 % sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The residue obtained after bulb tube distillation (210°C/2 mbar) is purified by means of flash chromatography on silica gel (hexane/ethyl acetate/toluene 3:1:4). The crude title compound is obtained in the form of an oil. ^{1}H-NMR ($CDCl_3$, ppm): 7.25 (m, 1H), 6.82 (s, 1H), 6.7-6.55 (m, 3H), 5.70 (m, 2H), 4.73 (s, 2H), 4.28 (q, J=7Hz, 2H), 3.81 (s, 3H), 2.98 (m, 1H), 2.65-2.3 (m, 4H), 1.32 (t, J=7Hz, 3H).

According to an alternative method, the title compound is obtained in a manner analogous to that described above from potassium 2-cyclopent-3-enyl-3-oxido-acrylonitrile:

Potassium 2-cyclopent-3-enyl-3-oxido-acrylonitrile: 5.0 g of cyclopent-3-enyl-acetonitrile are added, with stirring, to a suspension of potassium hydride (obtained from 28.1 g of potassium hydride 20 % dispersion in oil by washing twice with n-hexane) in 1:1 diethyl ether/hexane, gas evolution taking place. The brown suspension is stirred at room temperature for 1 hour and then 30.4 ml of ethyl formate are added dropwise over 15 minutes. The initially viscous suspension is stirred at room temperature for 12 hours and then filtered over a glass frit, and the coloured precipitate is washed with a small amount of hexane. The filter residue is dried at 50°C under a high vacuum for 3 hours and is then reacted, without further purification, with N-(3-methoxyphenyl)glycine ethyl ester as described in Example 44d).

d) 3-Amino-1-(3-methoxyphenyl)-4-(cyclopent-3-enyl)-*1H*-pyrrole-2-carboxylic acid ethyl ester: A solution of 18.2 g of [(2-cyclopent-3-enyl-3-nitrilo-propenyl)-(3-methoxyphenyl)-amino]acetic acid ethyl ester in 40 ml of absolute ethanol is added dropwise at room temperature, with stirring, to a solution of 1.41 g of sodium in 80 ml of ethanol. After 1 hour, the reaction mixture is concentrated, the residue is taken up in ethyl acetate and the organic phase is washed with 5 % sodium carbonate solution and saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The crude title compound is obtained in the form of an oil. ^{1}H-NMR ($CDCl_3$, ppm): 7.3-7.2 (m, 1H), 6.85-6.75 (m, 3H), 6.59 (s, 1H), 5.80 (m, 2H), 4.13 (q, J=7Hz, 2H), 3.81 (s, 3H), 3.35 (m, 1H), 2.85-2.75 (m, 2H), 2.5-2.35 (m, 2H), 1.27 (t, J=7Hz, 3H).

e) 7-Cyclopent-3-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ol: A mixture of 15.2 g of 3-amino-1-(3-methoxyphenyl)-4-(cyclopent-3-enyl)-*1H*-pyrrole-2-carboxylic acid ethyl ester and 40 ml of N,N-dimethylformamide dineopentyl acetal in 130 ml of chloroform is stirred at 70°C for 12 hours and then concentrated using a rotary evaporator. The oily residue is purified by means of flash chromatography on silica gel (hexane/ethyl acetate/-toluene, gradient 3:1:4 to 1:1:4). Reaction of 5.72 g of the resulting product in 150 ml of a saturated ammonia solution in methanol at 40-45°C for 48 hours and subsequent purification by means of flash chromatography on silica gel (methylene chloride/methanol 98:2)

yield the title compound in the form of a solid. ^{1}H-NMR ($CDCl_3$, ppm): 7.94 (s, 1H), 7.36 (m, 1H), 7.22 (s, 1H), 7.1-7.0 (m, 2H), 6.93 (m, 1H), 5.83 (m, 2H), 3.86 (s, 3H), 3.80 (m, 1H), 3.0-2.85 (m, 2H), 2.6-2.45 (m, 2H).

Example 78: 7-Cyclopent-3-enyl-5-(3-hydroxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

0.47 ml of boron tribromide is added dropwise at 0-5°C over 20 minutes, with stirring, to a solution of 0.5 g of 7-cyclopent-3-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine in 30 ml of methylene chloride. After 2 hours, a further 0.25 ml of boron tribromide is added dropwise and the mixture is stirred at 0-5°C for a further 2 hours. Subsequently, 5 ml of water are added to the reaction mixture, which is left to stand at room temperature for 2 hours. The coloured, two-phase mixture is filtered, the filtrate is adjusted to pH 7-8 by the addition of 1N sodium hydroxide solution and the resulting white precipitate is filtered off. The title compound is obtained in the form of a solid after recrystallisation from diethyl ether. ^{1}H-NMR (CD_3OD, ppm): 8.20 (s, 1H), 7.45-7.35 (m, 2H), 7.0-6.0 (m, 3H), 5.80, (m, 2H), 3.80 (m, 1H), 2.95-2.80 (m, 2H), 2.6-2.45 (m, 2H). FAB-MS: 293 $[M+H]^+$.

Example 79: 3-(4-Amino-7-cyclohexyl-pyrrolo[3,2-d]pyrimidin-5-yl)-phenol

^{1}H-NMR (DMSO-d_6, ppm): 9.98 (s, 1H), 8.20 (s, 1H), 7.35 (m, 2H), 6.87 (m, 2H), 6.79 (s, 1H), 5.70 (s (broad), 2H), 2.83 (m, 1H), 2.08 (m, 2H), 1.78 (m, 3H), 1.59 - 1.20 (m, 5H).

Example 80: 7-Cyclopentyl-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine hydrochloride

^{1}H-NMR (DMSO-d_6, ppm): 8.54 (s, 1H), 7.89 (s, 1H), 7.50 (t, 1H), 7.10 (m, 3H), 3.83 (s, 3H), 3.29 (m, 1H), 2.12 (m, 3H), 1.73 - 1.58 (m, 7H).

Example 81: 2-[(2-{4-[4-Amino-5-(3-methoxy-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethyl)-methyl-amino]-ethanol

A solution of 0.300 g 7-[4-(2-iodo-ethoxy)-phenyl]-5-(3-methoxy-phenyl)-5H-pyrrolo[2,3-d]-pyrimidin-4-ylamine in 2 ml methylamino-ethanol is stirred at 80 °C for 1.5 hours. The reaction mixture is concentrated using a rotary evaporator and the residue is triturated with diethyl ether. The title compound is obtained as white solid. ^{1}H-NMR (DMSO-d_6, ppm): 8.30 (s, 1H), 8.12 (m, 3H), 7.50 (t, 1H), 7.18 - 6.92 (m, 5H), 5.80 (s (broad), 2H), 4.10 (m, 2H), 3.86 (s, 3H), 3.86 (s, 3H), 3.64 (m, 1H), 3.49 (m, 2H), 2.97 (m, 1H), 2.80 (m, 2H), 2.30 (s, 3H).

a) 2-{4-[4-Amino-5-(3-methoxy-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethanol:
The title compound is prepared analogously to Example 14. ^{1}H-NMR (DMSO-d_6, ppm): 8,60 (s, 1H), 8.40 (s, 1H), 7.85 (d, 2H), 7.53 (t, 1H), 7,28 - 7.01 (m, 5H), 4.05 (t,2H), 3.84 (s, 3H), 3.75 (t, 2H).

b) 7-[4-(2-Iodo-ethoxy)-phenyl]-5-(3-methoxy-phenyl)-5H-pyrrolo[2,3-d]pyrimidin-4-ylamin:
8.26 g 2-{4-[4-Amino-5-(3-methoxy-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethanol, 3.42 ml diisopropyl ethylamine and 10.85 g methyl triphenoxyphosphonium iodide are added to 270 ml dimethylformamide and stirred at room temperatur for 2 hours. Then, the reaction mixture is poured onto water and extracted with ethylacetate. The organic layer is separated, extracted with saturated sodium chloride solution and dried with sodium sulfate. The solvent is removed using a rotary evaporator whereby the title compound is obtained as colourless crystalls. The title compound contains 50% 7-[4-(2-chloro-ethoxy)-phenyl]-5-(3-methoxy-phenyl)-5H-pyrrolo[2,3-d]pyrimidin-4-ylamine. ^{1}H-NMR ($CDCl_3$, ppm): 8.53 (s, 1H), 7.99 (m, 2H), 7.58 (s, 1H), 7.49 (t, 1H), 7.08 - 6.95 (m, 5H), 4.88 (s, 2H), 4.30 (t, 2H), 3.82 (t, 2H), 3.90 (s, 3H), 3,85 (t, 2H).

Example 82: 2-{4-[4-Amino-5-(3-methoxy-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethanol
The compound is prepared analogously to Example 81. ^{1}H-NMR (DMSO-d_6, ppm): 8.60 (s, 1H), 8.40 (s, 1H), 7.85 (d, 2H), 7.55 (t, 1H), 7.28 - 7.05 (m, 5H), 4.20 (t, 2H), 3.85 (s, 3H), 3.75 (t, 2H).

Example 83: 3-[4-Amino-7-[4-(2-hydroxy-ethoxy)-phenyl]-pyrrolo[3,2-d]pyrimidin-5-yl]-phenol
The compound is prepared analogously to Example 81.^{1}H-NMR (DMSO-d_6, ppm): 10.2 (s, 1H), 8.25 - 8.00 (m, 4H), 7.40 (m, 1H), 7.0 - 6.80 (m, 5H), 5.92 (s (broad), 2H), 4.00 (t, 2H), 3.7 (t, 2H).

Example 84: 2-{4-[4-Amino-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethanol hydrochloride

The compound is prepared analogously to Example 81. ^{1}H-NMR (DMSO-d_6, ppm): 8.59 (s, 1H), 8.49 (s, 1H), 7.85 (d, 2H), 7.54 (t, 1H), 7.25 (m, 1H), 7.16 (m, 2H), 7.07 (d, 2H), 4.05 (t, 2H), 3.85 (s, 3H), 3.75 (t, 2H).

Example 85: 7-{4-[2-(2-Methoxy-ethylamino)-ethoxy]-phenyl}-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

The compound is prepared analogously to Example 81. M.p.: 145 - 148°C.

Example 86: 5-(3-Methoxy-phenyl)-7-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-*5H*-pyrrolo[3,2-d]-pyrimidin-4-ylamine

The compound is prepared analogously to Example 81. M.p.:152 - 154°C.

Example 87: 7-{4-[2-(4-Fluoro-benzylamino)-ethoxy]-phenyl}-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

The compound is prepared analogously to Example 81. M.p.: 137 -140°C.

Example 88: 4-(2-{4-[4-Amino-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethylamino)-cyclohexanol

The compound is prepared analogously to Example 81. M.p.: 189 - 192°C.

Example 89: 5-(3-Methoxy-phenyl)-7-[4-(2-piperazin-1-yl-ethoxy)-phenyl]-*5H*-pyrrolo[3,2-d]-pyrimidin-4-ylamine dihydrochloride

The compound is prepared analogously to Example 81. ^{1}H-NMR (CD_3OD, ppm): 8.59 (s, 1H), 8.09 (s, 1H), 7.69 (d, 2H), 7.58 (t, 1H), 7.20 (m, 5H), 4.52 (t, 2H), 3.90 (s, 3H), 3.82 (m, 4H), 3.70 (m, 6H).

Example 90: 7-[4-(2-Dimethylamino-ethoxy)-phenyl]-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]-pyrimidin-4-ylamine

The compound is prepared analogously to Example 81. M.p.: 170 - 173°C.

Example 91: 1-(2-{4-[4-Amino-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethyl)-pyrrolidin-3-ol

The compound is prepared analogously to Example 81. M.p.: 132 -135°C.

Example 92: 2-{4-[4-Amino-5-(3-fluoro-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethanol hydrochloride

The compound is prepared analogously to Example 81. M.p.: 212 - 216°C.

Example 93: 7-[4-(2-Amino-ethoxy)-phenyl]-5-(3-fluoro-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

The compound is prepared analogously to Example 81. M.p.: 166 - 168°C.

Example 94: 5-(3-Fluoro-phenyl)-7-{4-[2-(2-methoxy-ethylamino)-ethoxy]-phenyl}-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

The compound is prepared analogously to Example 81. M.p.: 99.5 - 101.5°C.

Example 95: 5-(3-Fluoro-phenyl)-7-(4-{2-[(2-methoxy-ethyl)-methyl-amino]-ethoxy}-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine

The compound is prepared analogously to Example 81. M.p.: 152 -154°C.

Example 96: 2-2-{4-[4-Amino-5-(3-fluoro-phenyl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethylamino)-ethanol

The compound is prepared analogously to Example 81. M.p.: 148-151°C.

Example 97: 5-(3-Fluoro-phenyl)-7-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-*5H*-pyrrolo[3,2-d]-pyrimidin-4-ylamine

The compound is prepared analogously to Example 81. M.p.: 164 - 168°C.

Example 98: 5-(3-Fluoro-phenyl)-7-[4-(2-piperazin-1-yl-ethoxy)-phenyl]-*5H*-pyrrolo[3,2-d]-pyrimidin-4-ylamine

The compound is prepared analogously to Example 81. M.p.: 172 - 175°C.

Example 99: 4-[4-Amino-5-(3-hydroxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenol

The compound is prepared analogously to Example 81. ^{1}H-NMR (DMSO-d_6, ppm): 9.33 (s, 1H), 8.31 (s, 1H), 8.00 (m, 1H), 7.40 (m, 1H), 6.98 (m, 6H), 6.03 (s (broad), 2H).

Example 100: 3-[4-Amino-7-(4-{2-[(2-hydroxy-ethyl)-methyl-amino]-ethoxy}-phenyl)-pyrrolo-[3,2-d]pyrimidin-5-yl]-phenol

The compound is prepared analogously to Example 81. M.p.: 212 - 215°C.

Example 101: 3-{4-Amino-7-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrrolo[3,2-d]pyrimidin-5-yl}-phenol

The compound is prepared analogously to Example 81. M.p.: 212 - 216°C.

Example 102: 1-(2-{4-[4-Amino-5-(3-hydroxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethyl)-pyrrolidin-3-ol

The compound is prepared analogously to Example 81. M.p.: 218 - 222°C.

Example 103: 2-{3-[4-Amino-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethanol hydrochloride

The compound is prepared analogously to Example 81. ^{1}H-NMR (DMSO-d_6, ppm): 8.62 (s, 1H), 8.50 (s, 1H), 7.69 - 6.92 (m, 8H), 4.08 (t, 2H), 3.86 (s, 3H), 3.77 (t, 2H).

Example 104: 2-(2-{3-[4-Amino-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethylamino)-ethanol

The compound is prepared analogously to Example 81. M.p.: 166 - 168°C.

Example 105: 5-(3-Methoxy-phenyl)-7-[3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-*5H*-pyrrolo[3,2-d]-pyrimidin-4-ylamine

The compound is prepared analogously to Example 81. M.p.: 168 - 170°C.

Example 106: 7-[3-(2-Imidazol-1-yl-ethoxy)-phenyl]-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]-pyrimidin-4-ylamine

The compound is prepared analogously to Example 81. M.p.: 161 - 164°C.

Example 107: 5-(3-Methoxy-phenyl)-7-[3-(2-piperazin-1-yl-ethoxy)-phenyl]-*5H*-pyrrolo[3,2-d]-pyrimidin-4-ylamine hydrochloride

The compound is prepared analogously to Example 81. ^{1}H-NMR (CD_3OD, ppm): 8.53 (s, 1H), 8.19 (s, 1H), 7.22 - 7.10 (m, 8H), 4.53 (t, 2H), 3.92 (s, 3H), 3.80 (t, 2H), 3.72 (m, 4H), 3.31 (m, 4H).

Examples A-B: Pharmaceutical Compositions

Example A: Tablets, each comprising 50 mg of active ingredient:

Composition (10 000 tablets)	
active ingredient	500.0 g
lactose	500.0 g
potato starch	352.0 g
gelatin	8.0 g
talc	60.0 g
magnesium stearate	10.0 g
silicon dioxide (highly dispersed)	20.0 g
ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of the potato starch and the mixture is moistened with an ethanolic solution of the gelatin and granulated through a sieve. After drying, the remaining potato starch, the magnesium stearate, the talc and the silicon dioxide are mixed in and the mixture is compressed to form tablets each weighing 145 mg and comprising 50 mg of active ingredient, which may, if desired, be provided with dividing notches for finer adaptation of the dose.

Example B: Film-coated tablets, each comprising 100 mg of active ingredient:

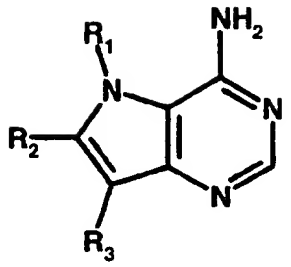
Composition (1000 film-coated tablets)	
active ingredient	100.0 g
lactose	100.0 g
corn starch	70.0 g
talc	8.5 g

calcium stearate	1.5 g
hydroxypropylmethylcellulose	2.36 g
shellac	0.64 g
water	q.s.
dichloromethane	q.s.

The active ingredient, the lactose and 40 g of the corn starch are mixed, and the mixture is moistened with a paste, prepared from 15 g of the corn starch and water (with heating), and granulated. The granules are dried, and the remaining corn starch, the talc and the calcium stearate are mixed with the granules. The mixture is compressed to form tablets (each weighing 280 mg), which are then coated with a solution of the hydroxypropylmethylcellulose and the shellac in dichloromethane (final weight of each film-coated tablet: 283 mg).

What is claimed is:

1. A compound of formula I



(I)

wherein

R_1 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl or cyclo-lower hydrocarbyl-lower alkyl, unsubstituted or substituted aryl or aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl or hetero-lower cyclyl-lower alkyl;

R_2 is hydrogen, lower alkyl or halogen;

R_3 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl or cyclo-lower hydrocarbyl-lower alkyl, unsubstituted or substituted aryl or aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl or hetero-lower cyclyl-lower alkyl;

or a salt thereof.

2. A compound of formula I according to claim 1, wherein

R_1 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl;

R_2 is hydrogen, lower alkyl or halogen;

R_3 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, unsubstituted or substituted aryl or aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl;

or a salt thereof.

3. A compound of formula I according to claim 1, wherein
R_1 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl;
R_2 is hydrogen, lower alkyl or halogen;
R_3 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, or unsubstituted or substituted aryl;
or a salt thereof.

4. A compound of formula I according to claim 1, wherein
R_1 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl;
R_2 is hydrogen;
R_3 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, or unsubstituted or substituted aryl;
or a salt thereof.

5. A compound of formula I according to claim 1, wherein
R_1 is unsubstituted or substituted lower alkyl or hetero-substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-lower alkyl, or unsubstituted or substituted hetero-lower cyclyl;
R_2 is hydrogen;
R_3 is unsubstituted or substituted lower alkyl, unsubstituted or substituted cyclo-lower hydrocarbyl, or unsubstituted or substituted aryl;
or a pharmaceutically acceptable salt thereof.

6. A compound from the group consisting of
5-isopropyl-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
5-cyclopentyl-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
5-(2-methoxy-ethoxymethyl)-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
5-[2-(2-methoxy-ethoxy)-ethyl]-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

(*4R/2S*) 4-(4-amino-7-phenyl-pyrrolo[3,2-d]pyrimidin-5-yl)-2-carbamoyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester;

(*4R/2R*)-4-(4-amino-7-phenyl-pyrrolo[3,2-d]pyrimidin-5-yl)-2-carbamoyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester;

5,7-diphenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

5-benzyl-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

5-(4-methoxy-phenyl)-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

5-(3-methoxy-phenyl)-7-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

4-(4-amino-7-phenyl-pyrrolo[3,2-d]pyrimidin-5-yl)-phenol;

3-(4-amino-7-phenyl-pyrrolo[3,2-d]pyrimidin-5-yl)-phenol;

7-[4-(2-benzyloxy-ethoxy)-phenyl]-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

2-[4-(4-amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-phenoxy]-ethanol;

7-[4-(2-imidazol-1-yl-ethoxy)-phenyl]-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-cyclohexen-1-enyl-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-cyclohexyl-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-cyclohexen-1-enyl-5-(3-hydroxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

5-phenyl)-7-(pyridin-3-yl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

4-{4-amino-7-[4-(2-imidazol-1-yl-ethoxy)-phenyl]-pyrrolo[3,2-d]pyrimidin-5-yl}-phenol;

3-{4-amino-7-[4-(2-imidazol-1-yl-ethoxy)-phenyl]-pyrrolo[3,2-d]pyrimidin-5-yl}-phenol;

7-[4-(2-imidazol-1-yl-ethoxy)-phenyl]-5-(4-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-yl-amine;

7-[4-(2-imidazol-1-yl-ethoxy)-phenyl]-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-yl-amine;

7-[4-(2-amino-ethoxy)-phenyl]-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

4-{4-amino-7-[4-(2-amino-ethoxy)-phenyl]-pyrrolo[3,2-d]pyrimidin-5-yl}-phenol;

3-{4-amino-7-[4-(2-amino-ethoxy)-phenyl]-pyrrolo[3,2-d]pyrimidin-5-yl}-phenol;

7-[4-(2-amino-ethoxy)-phenyl]-5-(4-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]-pyrimidin-4-ylamine;

7-[4-(2-amino-ethoxy)-phenyl]-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]-pyrimidin-4-ylamine;

2-{2-[4-(4-amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin7-yl)-phenoxy]-ethylamino}-ethanol;

4-(4-amino-7-{4-[2-(2-hydroxy-ethylamino)-ethoxy]-phenyl}-pyrrolo[3,2-d]pyrimidin-5-yl-phenol;

3-(4-amino-7-{4-[2-(2-hydroxy-ethylamino)-ethoxy]-phenyl}-pyrrolo[3,2-d]pyrimidin-5-yl-phenol;

2-2-{4-[4-amino-5-(4-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethyl-amino)-ethanol;

2-2-{4-[4-amino-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethyl-amino)-ethanol;

7-cyclohexen-1-enyl-5-(3-fluoro-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-cyclopentyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-cyclopent-1-enyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-cyclopent-3-enyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

3-(4-amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclopentanol;

3-(4-amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclopent-2-enol;

7-(3-methoxy-cyclopentyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-(3-methoxy-cyclopent-1-enyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

[3-(4-amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclopentyl]-methanol;

7-(3-methoxymethyl-cyclopentyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

4-(4-amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclopentane-1,2-diol;

7-(3-fluoro-cyclopentyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-(3,4-difluoro-cyclopentyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

3-(4-amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclohexanol;

3-(4-amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclohex-2-enol;

7-(3-methoxy-cyclohexyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-(3-methoxymethyl-cyclohexyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

4-(4-amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-cyclohexanol;

7-(4-methoxy-cyclohexyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-(4-methoxymethyl-cyclohexyl-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

5-phenyl-7-pyrrolidin-3-yl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-(1-methyl-piperidin-3-yl)-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

1-[3-(4-amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-pyrrolidin-1-yl]-ethanone;

5-phenyl-7-piperidin-3-yl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-(1-methyl-piperidin-3-yl)-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

1-[3-(4-amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-piperidin-1-yl]-ethanone;

5-phenyl-7-piperidin-4-yl-5*H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

7-(1-methyl-piperidin-4-yl)-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;

1-[4-(4-amino-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl)-piperidin-1-yl]-ethanone;

7-(5-methoxymethyl-pyrrolidin-3-yl)-5-phenyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
5-phenyl-7-(tetrahydrofuran-3-yl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
5-phenyl-7-(tetrahydro-thiophen-3-yl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
7-(1,1-dioxo-tetrahydro-thiophen-3-yl)-5-phenyl-5*H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
7-cyclopent-1-enyl-5-(3-fluorophenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
7-cyclopent-1-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
7-cyclopent-1-enyl-5-(4-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
7-cyclopent-1-enyl-5-(3-hydroxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
7-cyclopent-1-enyl-5-(4-hydroxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
7-cyclopentyl-5-(4-hydroxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
7-cyclopentyl-5-(3-hydroxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
7-cyclopentyl-5-(3-fluorophenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
7-isopropyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
5-(3-hydroxyphenyl)-7-isopropyl-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
7-cyclopent-3-enyl-5-(3-methoxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
7-cyclopent-3-enyl-5-(3-hydroxyphenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-4-ylamine;
2-[(2-{4-[4-amino-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethyl)-methyl-amino]-ethanol;
2-{4-[4-amino-5-(3-methoxy-phenyl)-*5H*-pyrrolo[3,2-d]pyrimidin-7-yl]-phenoxy}-ethanol; and
3-{4-amino-7-[4-(2-hydroxy-ethoxy)-phenyl]-pyrrolo[3,2-d]pyrimidin-5-yl}-phenol.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 and at least one pharmaceutically acceptable carrier.

8. A compound according to any one of claims 1 to 6 for use in a method for the therapeutic treatment of the animal or human body.

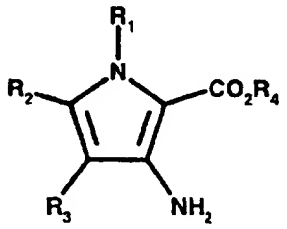
9. A compound according to any one of claims 1 to 6 for use in the treatment of diseases that are responsive to inhibition of the activity of tyrosine protein kinase $pp60^{c\text{-}src}$.

10. The use of a compound according to any one of claims 1 to 6 in the preparation of a pharmaceutical composition.

11. The use of a compound according to any one of claims 1 to 6 in the preparation of a pharmaceutical composition for the treatment of diseases that are responsive to inhibition of the activity of tyrosine protein kinase $pp60^{c\text{-}src}$.

12. A process for the preparation of a compound of formula I according to claim 1, which comprises

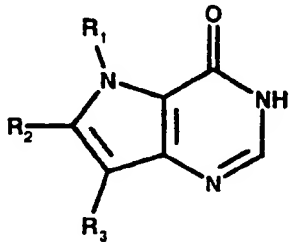
a) subjecting a compound of formula II



(II)

wherein

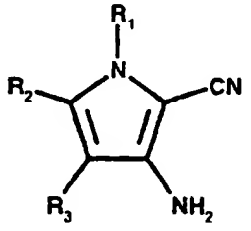
R_1, R_2 and R_3 are as defined in claim 1, and R_4 is lower alkyl, to a ring-closure reaction, with the formation of the pyrimidine ring, to give a compound of formula III



(III)

and replacing the oxygen by NH_2 by means of an exchange reaction; or

b) subjecting a compound of formula IV

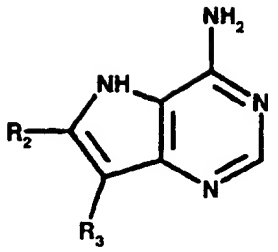


(IV)

wherein

R_1, R_2 and R_3 are as defined in claim 1, to a ring-closure reaction with the formation of the pyrimidine ring; or

c) reacting a compound of formula V



(V)

wherein R_2 and R_3 are as defined in claim 1, with a compound of formula VI

$$R_1—X \qquad (VI)$$

wherein R_1 is as defined in claim 1 and X is a leaving group;

and, if desired, converting a compound of formula I into a different compound of formula I, and/or, if desired, converting a resulting salt into the free compound or into a different salt, and/or, if desired, converting a resulting free compound of formula I having salt-forming properties into a salt.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 97/03115

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 A61K31/505 //(C07D487/04,239:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 10028 A (CIBA-GEIGY) 4 April 1996 see claims 1,13 --- -/--	1,7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
22 September 1997	30.09.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 97/03115

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 98, no. 13, 1983 Columbus, Ohio, US; abstract no. 107247m, O.S. SIZOVA ET AL.: "Pyrrolo[3,2-d]pyrimidine derivatives. IV. Synthesis, antibacterial and antitumor activity of 2,4,7-substituted pyrrolo[3,2-d]pyrimidines" page 598; XP002041395 see compounds of formula I & KHIM.-FARM. ZH. , vol. 16, no. 11, 1982, pages 1338-43, ---	1,7
P,A	WO 96 40142 A (PFIZER) 19 December 1996 see page 22, line 5 - line 16; claim 1 -----	1,7

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ...nal Application No
PCT/EP 97/03115

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		CA 2200210 A	04-04-96
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		FI 971225 A	14-05-97
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		NO 962386 A	09-12-96
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		SK 72996 A	09-04-97